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PROFESSOR E. D. ADRIAN enjoys an international reputation for his work on the physiology of sensation and the characteristics of nervous action. From 1929 to 1937 he was Foulerton research professor of the Royal Society, and since 1937 he has occupied the chair of physiology at Cambridge. In 1932, Adrian was awarded (with Sir Charles Sherrington) the Nobel Prize for Medicine in recognition of his work on the function of neurones. In recent years he has done much to further the use of the electroencephalograph in Britain, and he was elected president of the recently established Electroencephalographic Society. In addition to his numerous contributions to scientific journals, much of his work has been summarized in two important books on *The basis of sensation* (1928) and *The mechanism of nervous action* (1932). Adrian has been made an honorary fellow of numerous foreign scientific societies, and in 1942 he was admitted to the British "Order of Merit" (O.M.), which is limited to 24 members.

DR. F. M. R. WALSH has been associated with University College, London, during the whole of his medical career. He qualified at University College Hospital in 1910 and served as consulting neurologist to the Army during the war of 1914-18. He is physician to the National Hospital, Queen Square, physician in charge of the neurological department, University College Hospital, and neurologist to the Hospital for Tropical Diseases, Greenwich. Walsh's many contributions to neurological literature include a textbook—*Diseases of the nervous system* (4th edition, 1945), which first appeared in 1940, and has rapidly become established as a standard work—and papers on the physiology and pathology of the nervous system. He is also editor of *Brain*, which was founded in 1878 and is probably the oldest of the world's neurological journals. Walsh is also known as a stimulating and sometimes provocative contributor to the medical press of articles and letters on more general subjects. These contributions show that he shares Claude Bernard's suspicion of the tendency to regard experiment as a substitute for thought.

PROFESSOR GEOFFREY JEFFERSON studied at Manchester University, graduating in medicine in 1911. During the 1914-18 war he was a surgical specialist to the British Expeditionary Force. In 1924 he was appointed Hunterian professor of the Royal College of Surgeons, and is now professor of neurosurgery and lecturer in applied anatomy at the University of Manchester. He is also consultant adviser in neurosurgery to the Ministries of Health and Pensions, and was formerly honorary surgeon to the National Hospital, Queen Square. Jefferson's numerous writings consist mainly of papers on neurosurgical and general surgical subjects. He has also contributed important chapters to Carson's *Modern operative surgery* and Choyce's *System of surgery*. Neurosurgery has good claims to be regarded as the most scientific of the surgical specialities, but although it is by no means the most recent of these, the number of full-time neurosurgeons is still very small. Jefferson is internationally recognized as one of the leaders in his subject.

PROFESSOR HUGH W. B. CAIRNS was born in Australia and studied medicine at the University of Adelaide. During the 1914-18 war he served in the Australian Army Medical Corps. He went to Oxford as a Rhodes scholar, where his work in Sir Charles Sherrington's laboratory led him to take a special interest in the nervous system. He is at present Nuffield professor of surgery and surgeon to the Radcliffe Infirmary, Oxford, consulting surgeon to the London Hospital, and consulting neurosurgeon to the Army, in which he holds the rank of Brigadier. In 1925 he was appointed Hunterian professor of the Royal College of Surgeons, and during the next two years visited the U.S.A. as a Rockefeller travelling

fellow, where he had the opportunity of studying under the great Harvey Cushing. Returning to England, Cairns started at the London Hospital the first exclusively neurosurgical clinic in the country, since when he has done important work on cerebral tumours and brain abscess. During the war, most of his time has been devoted to the study of head injuries and their treatment, and he has the unusual advantage of working at a military hospital which may have in its wards as many as 200 cases of head injury at the same time.

AIR VICE-MARSHAL C. P. SYMONDS is physician in charge of the department of nervous diseases, Guy's Hospital, physician to the National Hospital, Queen Square, and a member of the Medical Research Council's Committee on Mental Disease. At present he is serving as consulting neurologist to the Royal Air Force, and in this capacity has made numerous journeys abroad to advise on neurological problems of warfare. After training at Guy's Hospital he became medical registrar there before being awarded a Radcliffe travelling fellowship at Oxford University. During the last few years he has devoted particular attention to the neurological aspect of head injuries.

WING-COMMANDER DENIS WILLIAMS is registrar at the National Hospital, Queen Square. He was educated at the University of Manchester and has held a Halley Stewart research fellowship at the National Hospital, a Rockefeller travelling fellowship in neurology, and an honorary research fellowship at Harvard University. He has for several years been interested in the clinical application of electroencephalography, and has made considerable contributions to the literature on this subject. Williams is now serving as a neurologist in the medical branch of the Royal Air Force.

DR. AUBREY LEWIS received his medical training at Adelaide, Baltimore and Heidelberg, qualifying in 1923. He was medical registrar at Adelaide Hospital and house physician at Johns Hopkins Hospital, Baltimore, and from 1926-28 was a Rockefeller medical fellow. He is at present clinical director and lecturer in psychiatry at the Maudsley Hospital—the headquarters London County Council mental hospital and clinic which became, under the direction of the late Prof. Edward Mapother [1881-1940], an important centre of neuropsychiatric teaching and research. There are few branches of medicine which provide so many incentives to the two extremes of system building and blind empiricism, but Lewis has the reputation of combining a cool judgment with a vigorous intellect. He is also examiner in psychological medicine, London University, and consultant in psychological medicine at the British Postgraduate Medical School, Hammersmith.

DR. K. J. W. CRAIK graduated in philosophy at Edinburgh University in 1935, and was demonstrator in the psychological department of the same university during 1935-36. From 1936 to 1939 he was engaged in research at the psychological laboratory, Cambridge, mainly on visual adaptation and on the correlation of subjective and neural investigations of sensory processes.

During the war he has worked for the Medical Research Council, Ministry of Supply, Admiralty, and Air Ministry, on visual problems and questions of gun laying and hand- and eye-coordination. He is director of the Medical Research Council Applied Psychology Research Unit which has recently been established in Cambridge. He is particularly interested in problems of instrument- and machine-design from the point of view of convenient and safe operation. He has also been concerned with dark-adaptation as a test for nutritional deficiency, and he has published about 25 scientific papers in psychological and physiological journals and a book on *The nature of explanation* (1943).

REVIEW OF SELECTED PAPERS. Contributions to this section have been received from Dr. E. Guttman, Dr. W. M. Honeyman, Mr. A. Sutcliffe Kerr, Dr. Aubrey Lewis, Mr. D. W. C. Northfield, Dr. A. Paterson, Dr. W. Rees, Lieut.-Col. W. Ritchie Russell, Professor Arnold Sorsby, Dr. N. Southwell, Wing Commander Denis Williams and Dr. R. Wyburn-Mason.

SPECIAL CONTRIBUTIONS

PHYSIOLOGICAL MECHANISMS IN THE BRAIN*

Professor E. D. ADRIAN, O.M., F.R.S.

Physiological Laboratory, Cambridge

The physiology of the central nervous system has made rapid progress in the past ten years, but we are still at a stage when it is easier to accumulate observations than to decide which are significant. It may help us to do so if we are constantly reminded of some of the routes by which neurology has already advanced. That is the aim of the present discussion, and it has been written in the hope that it may lead others to similar speculations on the prospects of neurological research.

* [Based on the Pilgrim Trust Lecture delivered to the National Academy of Sciences at Washington on April 24, 1944.]

Part of the difficulty in assessing results lies in the complexity of structure and the imposing functions of the system we are studying. For the physiologist, who is not primarily concerned with disease or injury of the nervous system, the general objective of his research must be to explain how our movements are controlled by the mass of nerve cells which make up the brain and spinal cord, and a more remote objective, but one which cannot be disregarded, is to explain how these nerve cells control or are controlled by our minds. This latter aim may be unattainable—it raises the old philosophical problem of the relation of mind and matter, but the

neurological approach to it may bring new arguments. With so ambitious a programme it is no wonder that we cannot always tell what is the best line of advance.

Detailed knowledge of the brain is all of very recent date. It was known to Descartes that the brain was in touch with the nerves from the sense organs, but up to 1860-70 there was nothing to show what sort of events took place in it. Then came the discovery of the speech centres by Broca and of the motor area by Fritsch and Hitzig, and with that the search for mechanism in the brain could really begin. There were definite pathways and cell-groups for particular operations, for the comprehension of words, for skilled movements and so on. The brain came to be thought of as a great mass of nerve cells and interlacing fibres, and the tracing of pathways through it became the main task of the neurologist—a task which is now nearing completion.

Sherrington and Pavlov

Between that time and the present, one of the major developments came from Sherrington's work on the spinal reflexes, described in his well-known book—*The integrative action of the nervous system*. He contrived to make the reactions of the spinal cord intelligible by analysing them into their simplest components. To achieve simplicity, the spinal cord was isolated from the brain which normally directs it. The spinal reflexes are therefore the reactions of a mutilated fragment of the nervous system and they are produced in a thoroughly artificial setting. But Sherrington's study of them showed, first, that in those simplified conditions they could be produced with mechanical regularity, and second, that these simple reactions could be combined together so as to build up much more elaborate patterns of activity. After this it seemed much more reasonable to speak of the mechanism of the spinal reflexes and to suppose that more complex behaviour might come of their integration. Sherrington himself was content with the activities which do not involve the cerebrum and would always be classed as reflex in spite of their complication—adjustments of posture and locomotion for instance. The cerebrum seemed to him to introduce quite a different order of complexity, and it was Pavlov who developed the idea of a truly mechanical brain, pointing out that we cannot expect to understand the mechanism which underlies behaviour if we speak or think of it in terms which imply the mind.

Pavlov's teaching, like Freud's has been publicised too much and has suffered from it. It has left an enduring mark on neurology, but much more as the basis of a particular technique of research than as the basis of a philosophy. For, in the present period, new information about the working of the brain has been accumulating at such a rate that the theories are scarcely worth making. As usual in physiology, the new information has come as the result of technical improvements in other fields, in brain surgery, in experimental psychology and particularly in the detection of small electric currents. It is with the last-mentioned technique that the following account is concerned.

Recording Electrical Activity

First of all we have had far more detailed studies of the mechanism of reflexes. Sherrington stimulated nerves and recorded the reflex contractions of individual muscles. In this way he could tell how faithfully the signals coming out of the cord to the muscles copied those which he had sent into it—whether the reflex pathway seemed to have inertia and what sort of changes occurred in it. But nowadays the signals which enter and leave the cord can be split up into the individual nerve impulses of which they are composed. These are recorded electrically and their appearance can be timed to a ten-thousandth of a second on the sweep of a cathode-ray tube. Recording the electric changes which accompany nervous activity is an old story. It was used by Gotch and Victor Horsley 50 years ago to trace the pathways of conduction from the brain to the cord, but the modern development, started by the work of Gasser and Erlanger at St Louis, has now reached such precision that we can make an accurate time-table for each pulse of activity. And with microelectrodes the search can be carried deep into the cell masses of the grey matter. But the outcome is still the same. When the conditions are standardized we find an exact precision of response within the central nervous system, a mechanical regularity extending to the units as well as to the summed effect of the whole mass of nerve cells and fibres.

But very naturally the reactions which are submitted to this kind of minute analysis are not a random sample. They are selected just because there is some chance that the analysis can be made, and nearly all of them have been reactions of the local executive parts of the nervous system, the spinal cord and the brain stem. If these parts are not directed by the brain the animal does act—or react—as if it were an automaton, with a mechanical regularity which allows us to predict exactly what it will do in the circumstances. In the intact animal there is the same local mechanism of nerve cells and fibres in the cord, but it is made use of by the brain to bring about an entirely different sort of behaviour—one which seems far less automatic. A brainless cat will lift its foot each time the skin is pinched, but a normal cat may do almost anything and will probably do something different each time. Evidently when the brain is in control the connection between incoming and outgoing signals is far more obscure.

Limitations of Knowledge of Brain Mechanisms

Here we are still on the outskirts. A great deal is known about the nervous pathways in the brain and about the sort of activity which takes place in the nerve cells, but it does not get us very far. We are dealing with what seems to be no more than a great sheet of nerve cells linked by nerve fibres to some central cell masses and to the rest of the nervous system. We can be fairly certain, too, that its working must depend on the spatial distribution of activity in it. This is determined by the particular pathways which must be taken by the incoming and outgoing messages, for the messages are all in the same form wherever they come from, and it is because they arrive in different regions that we interpret one as sight and another as sound. Thus, if we look at a bright cross we can be reasonably certain that the initial event in the brain will be the development of cellular activity in a more or less cross-shaped area at the back of the occipital lobe, and if we listen to a voice the same kind of activity will appear in the temporal lobe with a pattern, in space and time, corresponding to the areas of vibration in the cochlea. Probably each smell will influence the olfactory area in a similar way and we can be fairly certain that all these different pictures—of visual, auditory, olfactory and tactile stimuli—are made up of the same elements, rapid sequences of nerve impulses distributed more or less thickly over the receiving areas and calling up more or less activity in the nerve cells there.

The detailed mapping of the patterns formed in the brain by the sense organs—the patterns which mirror the external world—is an achievement of the last few years. But it tells us only about the way in which information is sent into the brain and not about the way in which the brain reacts to it. In fact, the mapping has to be done in a brain which is anaesthetized so that the sensory picture can stand out against a quiet background. Otherwise there would be a constantly changing activity to confuse the map. It is this activity, in all parts of the brain, which should tell us how the sensory pictures are recognized and used to guide our behaviour, but to analyse it we need to know what is going on in the brain of a conscious subject.

Here there are only some odd scraps of information. The difficulties seem to be mainly technical. As far as we can tell, any change in nerve-cell activity should produce a corresponding change in the electric currents in the surrounding medium, and if we could record at will from any group of nerve cells in the brain we should be in a fair way to knowing what happens when a new sensory picture is thrown on the cortical surface. But in a man with an intact skull we cannot place electrodes in immediate contact with the brain and so we can only record the average of all the electric changes over a fairly large area—the average activity of several million nerve cells and not the exact events in each. It is remarkable that such an average should give anything that can be recorded, but that it does so was shown 16 years ago by Hans Berger. Berger found that in a subject at rest and with eyes closed a regular series of potential-waves could be detected by electrodes on the head. These come from the cerebral cortex and indicate an activity in the nerve cells over a fairly large area. But unfortunately Berger's α rhythm seems to be some sort of basic activity of the undisturbed brain. It has a fixed frequency (8-10 per second) and disappears as soon as visual attention is aroused. Thus the α waves cannot tell us much about the specific activities by which the brain

patterns are analysed. One thing they can do is to show something of the nervous processes which underlie a shift of attention from one field to another. In man for instance, where vision is the predominant sense, the rhythm comes and goes whenever the attention is transferred from the visual field to the auditory and vice versa. From the size and distribution of the waves, therefore, we can form some idea of the extent of the brain surface which may be normally involved in vision and hearing.

Flicker Rhythms

The α waves show us no more than the basic rhythm of those parts of the brain which are awake but have little to do.

But there is a further development which tells us something about the specific activities of the visual regions. It depends on forcing the nerve cells to work in unison by illuminating the field with a flickering light. When this is done, the potential-changes over the occipital region have a frequency corresponding to that of the flicker and are large enough to record through the skull. We have therefore what amounts to a method of tracing the visual signals in the brain, for we can make them fairly easy to recognize as long as the time-sequence is preserved.

These flicker rhythms seem to reveal an interesting borderland between the primary visual area and the rest of the brain. In this borderland (which extends well beyond the boundaries of the occipital lobe) the spatial as well as the temporal pattern of the excitation is preserved to some extent, but the spread of the visual signals into it is governed partly by the degree of attention given to the visual field, for the diversion of attention to another task will often disorganize the rhythm. And there are all sorts of interactions between the flicker rhythm and the α rhythm, which tends to reassert itself when attention weakens, and may combine with the flicker rhythm, if the two frequencies are suitably related, or may supplant it altogether.

Another point about the activity in this borderland area is that it is far from being an exact copy of the patterns of light and shade which fall on the retina. There is evidence of a good deal of interaction, not only between different points on the same side of the brain but between the two sides. For instance if we look at a field of which only the right or the left half is flickering, the flicker potentials will appear on the opposite side of the head—this is where the signals of the flicker would arrive. But if the two halves of the field are made to flicker at different rates, the brain seems to give up the unequal struggle and produces a confused medley of frequencies much the same on both sides.

In interpreting results of this sort it is very easy to be misled, for it is a long way from a flickering screen to the occipital lobes, and a still longer way from there to the mind. The flicker waves do seem to be somewhere on the direct route, however, for when they change in rate or regularity there is usually a change in the sensation which has the same direction, faster or slower, though we may not be able to analyse it more precisely. Unfortunately, with present

techniques, the method can be applied only to visual events. A repeated noise like that of a machine gun does not give a corresponding series of potential waves in the auditory area large enough to detect through the skull—either because they are not developed over a large enough area or because the area is unfavourably placed. It seems, therefore, that the present technique of recording brain events, by oscillographs connected with electrodes on the head, is not likely to lead very far. But such a technique may soon be superseded, judged by the standards of modern physics it is already obsolete, and I think we should look forward to the possibility of being able to record all the electrical events—the changing potentials and ionic movements—within the brain in far greater detail and without hindrance from the skull.

Future Paths in Neurophysiology

What can we expect if such a development occurs, as I think it is bound to do sooner or later—when we can study the whole changing pattern of activity in the cerebral hemispheres from moment to moment?

It will not necessarily tell us much about a most important and characteristic property of the brain, its power of learning, of forming associations or conditioned reflexes, for this must depend on changes which are persistent and may not give rise to electrical effects. In fact it may need a biochemical and histological survey to show us why the dog comes to salivate whenever the dinner bell is rung. But an electrical survey could scarcely avoid giving some entirely novel information about what is happening in the brain when we think or solve problems or decide what to do. The progress of neurology has been full of surprises and it is not wise to predict, but sooner or later we are likely to reach a position where some very fundamental problems ought to arise. For example—in the brain of a conscious man, will there be the same mechanical precision in the response of nerve cells and cell masses to the signals which reach them?

I have an uneasy feeling that we shall find a catch somewhere. The problem may become more and more meaningless as we seem to come nearer to it, or perhaps it will become obvious that it is not one which could ever be solved by beings like ourselves. However, we can be quite certain of one thing: whatever the final outcome of enquiries about the mechanism of the brain there is an immense amount waiting to be found out on the way, and almost within our grasp even now. Before the war the younger generation of neurophysiologists were advancing at a pace which accelerated every year, and those of us who dated back to the string galvanometer were already out of breath. When they come back again we may confidently expect to be left so far behind that these philosophic doubts will be our only consolation. The alchemists may have wasted their time in futile attempts to reach a goal which was not there, but they were the fore-runners of the chemists. In the same way the search for the mechanisms of the brain, though its goal, as we see it now, is perhaps unattainable, may lead us to a new understanding of human behaviour.

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“QUEEN SQUARE” THE CRADLE OF BRITISH NEUROLOGY

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Since the National Hospital was founded in Queen Square nearly three-quarters of a century ago it has had a unique and unbroken record of achievement in each of its three fields of activity, the care of the sick suffering from affections of the nervous system, research into nervous diseases and allied problems of neurophysiology, and the training of neurologists. Wherever in the world neurology is studied, “Queen Square,” as the hospital is familiarly known, has become a household word.

A remarkable succession of men of genius have served on its medical staff, and have by their labours and repute built up a school of neurology of which British medicine may well be proud. They include Brown-Séquard, Hughlings Jackson, Ferrier, Beevor, Gowers, Horsley, Bastian, Gordon

Holmes and Kinnier Wilson, to mention only the outstanding names. The hospital staff has numbered more Fellows of the Royal Society on its clinical staff than any other British hospital save one—University College Hospital.

From its wards and laboratories there has flowed a steady stream of original work, some of it of classical importance, while as a teaching centre it has attracted postgraduate students from all quarters of the globe, and has played a remarkable part in the training of generations of neurologists here and abroad.

For a small hospital that was, until comparatively recently, but poorly endowed with what are ordinarily regarded as adequate facilities for research and teaching, this is a remarkable record, and one that lends point to the oft forgotten

truth that it is round the man, and not round the plan or the material resources, that the wheels of research revolve most rapidly and fruitfully

Scientific knowledge consists in more than the sum total of factual data available at any given time. It includes, and must include if it is to be truly scientific, the interpretation and synthesis of facts, the forming and testing of hypotheses. As Hughlings Jackson, the "deepest thinker in neuropathology of the nineteenth century" as Arnold Pick has called him, emphasized many years ago, "we have multitudes of facts, but as they accumulate we require organisations of them into higher knowledge." This balance of original observation and of interpretation and generalization is one of the rarer accomplishments in scientific endeavour, and one of Queen Square's chief claims to an honoured place in the history of modern medicine is the contribution it has made to ordered knowledge and to ideas in neurology. For this we are, of course, mainly indebted to Hughlings Jackson, whose contributions have a philosophic quality nowhere surpassed in medicine at any time. His approach to the subject of "convulsions beginning unilaterally," or Jacksonian convulsions^{18 19} as they have come to be widely known, is a case in point. He was not content with the minute observation and description of these phenomena. Of equal or even greater interest to him was the light they threw upon the localization of motor function in the brain, and upon the nature of this localization.

Jackson was indeed the discoverer of the fact of the topographical localization of function in the cerebral motor cortex, at a time when physiologists were denying that any such localization obtained, and the pioneer work of Fritsch and Hitzig⁶ in Germany and of Ferrier in this country did but confirm the inferences drawn by Jackson²⁰ from clinical observation. But while these and later experimental researches surpassed in completeness and delicacy the "mapping" of this localization of functions within the cerebral cortex, Jackson's analysis of the mode of representation* still remains the most profound and the most satisfactory. Of similar quality were his original observations upon disorders of the speech function due to cortical lesions.²⁰ From these he drew the inference that referential and emotive speech must be separately considered, he differentiated the receptive from the expressive aspects of speech, and amongst his many aphorisms is the one that states that "the unit of speech is the proposition."

Of even wider scope were Jackson's teachings upon the evolution and dissolution of function in the nervous system.²² He developed the conception of physiological levels of function, each superimposed upon the one lower in the hierarchy and embodying a re-representation of the functions subserved by it. The lowest level, which he thought of as subcortical, embodied in each of its units a relatively fixed and restricted representation of function, let us say of motor function. The fixed reflex reactions at the brain-stem and cord constituted this level. Above it is the second level, of which the cerebral motor cortex—the excitable "cortex of Sherrington"²³ and the earlier physiologists—is the substratum. Herein movements and not muscles are represented, but the representation is of wider scope and leaves more room for variability in response than in the lowest level. Unlike the experimental physiologists, Jackson never envisaged the fixed "mosaic" type of representation of movements in the cerebral cortex which still largely holds the field in current opinion. He believed that sensory and motor processes—not anatomical parts—are represented in the cortex,²¹ but that when we look at the problem anatomically, it can be said that such a mobile organ as the hand with its digits is represented—in respect of its motor activities—in all parts of the excitable motor cortex, but that there is a focus in which this representation is maximal, and is the principal function of that focus. Thus it is that, when the so-called hand area of the motor cortex is destroyed by disease, or excised by the surgeon or experimental physiologist, there yet remains a considerable representation of the movements of that part outside the excised area. It is this persisting representation that accounts for the transience of paralyses of cortical origin. Yet this remaining representation does not wholly compensate for the movements lost, and careful investigation will reveal the loss of some movements.

Jackson placed the highest level of representation in the

frontal lobe, anterior to the excitable region of the cortex. Within a unit of this representation, virtually all motor activities were present, but in somewhat different arrangement. Thus apraxia, aphasia, and perhaps the striking general immobility that may characterize subjects suffering from frontal-lobe lesions, represent highest-level types of paralysis. Here, high-level functions are paralysed—not relatively restricted movements, as after damaging lesions of the motor cortex, or the still more restricted movements of groups of muscles as in lowest-level lesions.

The higher the level of function, the less deeply organized did he suppose it to be, and the more vulnerable to destroying processes. Thus, he classified movement into extremes of "most voluntary" and "most automatic" categories. The former were the first to undergo dissolution in destroying lesions, the latter the last. Thus, dissolution is the reverse of evolution.

Jackson also expounded the doctrine of "release of function"²² in destructive lesions of the central nervous system. The destruction of a high-level function, say that of the motor cortex, leads not only to loss of movements—a negative symptom—but also to the release and consequent overaction of subordinate motor mechanisms—positive symptoms. The paralysis and the hypertonus of a residual hemiplegia represent respectively these two categories of symptoms. Thus, as he pointed out, a purely negative, destructive lesion cannot account for overaction, but it allows this to occur from uncontrolled activity of persisting and intact elements of the motor mechanism.

These brief summaries exemplify but a few of the generalizations that Jackson made, and to have been the laboratory, as it were, of a genius of this high order must secure for the National Hospital a permanent place in the history of medicine in our time. The full harvest of his labours has not yet been fully garnered, but his influence continues to grow in the world of neurology.

The essence of Jackson's rare genius was that he was never content to record new facts, but he brought to their interpretation and to their synthesis those intellectual instruments by which alone ordered knowledge is forged from crude facts. This rhythm of observation and interpretation is the essence of truly scientific thought, and indeed of scholarship in all its fields.

Amongst Jackson's contemporaries at Queen Square was Charlton Bastian whose name was familiar to an earlier generation as the author of studies on disorders of the speech function.²⁴ He was the first to describe the syndrome of complete transection of the spinal cord.³ He also first described the syndrome of flaccid paralysis with loss of tendon reflexes and retention of urine, and contrasted it with the syndrome of spastic paralysis with increased reflexes which is characteristic of incomplete lesions of the cord.

David Ferrier, after the completion of his distinguished career as an experimental physiologist and one of the pioneers of the study of cerebral cortical function,⁵ joined the staff of the hospital as a physician, and helped to maintain that scientific and physiological outlook upon clinical neurological problems that has always been the tradition of the hospital. Thus its name is intimately associated with both clinical and experimental research on cortical function. This tradition was further developed by Victor Horsley, surgeon to the hospital, whose many experimental studies of the cerebral cortex^{7 17} of apes have their place in the history of this subject.

In addition, Horsley, at Queen Square and at University College Hospital, laid the foundations of neurosurgery.¹² No one would deny that this has undergone a great development at the hands of Cushing and his disciples in America and in Britain, and that surgical interventions on the brain can now be safely and successfully undertaken that were impossible in Horsley's day, but those who can still recall the picture of Horsley removing a meningioma or dividing the sensory root of the trigeminal nerve will pay tribute to the supreme technical skill that he was able to display with relatively primitive instruments. Side-by-side with his surgical work, Horsley continued for many years to undertake experimental work on the brain, and with Clarke devised the stereotaxic instrument that has since proved so effective in the hands of workers of a later generation.

Of another order of genius was Sir William Gowers, the acute clinical observer of an unrivalled and carefully marshalled experience, the inspiring and forceful teacher and the

* [see also BMB 619]

author of a textbook¹¹ that yet remains unsurpassed in the richness of its clinical detail, and the clarity of its writing. Though this work is now 60 years old and has not been revised for nearly that time, the clinical neurologist can still turn to it with advantage for reliable and minute descriptions of clinical states. For example, Gowers' description of hemiplegia in all its phases, from initial to residual, is of a completeness and lucidity that has not so far been equalled in more modern works. Other classic books from his hand are his volume on epilepsy¹⁰ and the still more fascinating monograph entitled *The border-land of epilepsy*¹², in which epilepsy, migraine, and the syndrome he named "vaso-vagal attacks" are described and compared. He also wrote the first textbook on medical ophthalmology⁹ and was the first physician to develop the use of the ophthalmoscope in general medicine. Those of an earlier generation may recall Gowers' haemoglobinometer,⁸ an example of his versatility over the whole field of medicine.

Coming to more recent achievements, we may mention the first complete clinico-pathological account of the malady we now know as subacute combined degeneration of the cord, the work of three physicians of the hospital, J. Collier, F. Batten and J. Rusien Russell.²⁵

To Kinnier Wilson²⁷ we owe the development of our modern clinico-pathological knowledge of affections of the corpus striatum, as first expounded in his well-known paper on

the malady he entitled progressive lenticular degeneration.²⁴ The association of hepatic and cerebral lesions was first brought to notice in this paper, which has inspired a very considerable literature since it first appeared in 1912.

To Gordon Holmes, neurology owes studies of the first importance upon the cerebellar symptom-complex,¹⁴ upon the minute localization of vision in the area striata of the cortex^{18, 28, 24}, upon gunshot wounds of the spinal cord, with Henry Head upon sensory disturbances following cerebral lesions, and upon a wide range of other clinical and pathological problems in neurology.

Throughout the entire period thus briefly reviewed, there has been an active school of neuropathology to which large numbers of graduates from America, Europe and the British Dominions, as well as from the United Kingdom, have been attracted, and this school continued in full activity up to the outbreak of the present war.

At no time in its history has the hospital lapsed into a mere institution for the care of the sick. The foundation of a new research institute, made possible by the generosity of the Rockefeller Foundation in 1938, and the endowment of a neurological research unit by the Medical Research Council, have now provided the hospital with facilities for the continuance and expansion of its work that augur well for the future, and offer the prospect that it will continue to maintain its traditions in the postwar years.

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PLANNING FOR HEAD INJURIES

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Had we looked at Britain just before the present war commenced we should have observed that a number of neuro-surgical centres had arisen, based on the university medical schools. Most of these were recent or new creations and had been planted only long enough to get firm roots. They

were not sufficiently long established to have grown a number of transplantable shoots. However we had shown a greater tendency than any other European country to establish specialized departments for the surgical care of diseases of the brain and spinal cord. We had early recognized that

neurosurgery was a whole-time, and indeed a life-time's, work, we had outgrown our earlier, and the longer-surviving Continental, method, whereby the professor of surgery did, when he had time, what the professor of neurology or the physician directed. When the war came we were full of anticipatory interest, hoping that the neurosurgeon would this time be able to contribute no little to the care of the battle-casualty. Our expectation was the greater because, in the last war, no pure neurosurgical units were established early and by order, though two or three sprang up unofficially as the years passed.

Special Neurosurgical Centres

Before the outbreak of war it was obvious that special conditions of medical work would be created by air-attacks on civilians. This war would be of a new kind, worse than any before because something was going to happen that all Peace Conventions have prohibited—the killing and injuring not only of the men of the fighting services, not only of the non-combatant male civilian population, but of women and children. Nor would hospitals and their staffs be in any way immune from disaster. We knew what to expect from our adversaries' record, and from their declared intentions to those who opposed them. Work could not be carried out in the hospitals in the great cities, certainly not in London, and it was considered that London would be the principal and earliest target. Innovations were therefore planned at Cabinet direction by a new division of the Ministry of Health—the Emergency Medical Service (EMS), which drew up a scheme that has worked well. By this plan, London was divided into radial Sectors each derived from a teaching hospital. The rest of the country was divided into Regions. Specialist advice was sought for different branches of medicine and surgery. In the first instance Professor H. Cairns was neurosurgical adviser to the EMS. At the outbreak of war we divided England between us, but when he went to the Army in February 1940 the present writer took over England and Wales. Two neurosurgical centres were first established north and south of London, and a third in the north-west. The famous National Hospital, Queen Square, was closed for surgery, and its surgical division moved into the country. One ward at Queen Square was later burned by incendiaries, and the Hospital was hit by a bomb that luckily did not explode, but otherwise it remains [at the time of writing] intact and its staff unhurt. The other two London neurological hospitals (Maida Vale and the West End) were also much modified in their working, one in fact was eventually destroyed, the other badly damaged.

During the first nine months of the war, London continued to be regarded as the most vulnerable of British targets because of its size and its nearness to the Continent. But after the fall not only of France but of most of Europe (by conquest or by seduction), it became plain that the new bases that the enemy now possessed made the whole country vulnerable. This possibility was soon turned into fact. To meet the needs of the population the country had already been divided up into Regions with a great number of new hospital beds, mainly outside the great cities. Some of these were designated Special Centres, and, stage by stage, 10 Special Head Centres were set up in England and 2 in Scotland (the latter under the Scottish Board of Health). Most of them were originally replacements of the peace-time centres moved to safer places, but some were new. These 12 centres did not all come into being at once, they have been developed to meet needs. The latest were added only in the summer of 1944 for the invasion of Europe, when 3 temporary centres were created to deal with gun-shot wounds of the head arriving from the Normandy battles. Circumstances have caused all of these centres to become extremely important to their Sectors (London) or Regions (the rest of Britain, i.e. the larger part). The centres vary in size from 60 to 80, or even 120, active beds in each. The staff has been 1 chief neurosurgeon, 1 chief assistant, 2 house surgeons, 1 anaesthetist, 1 pathologist, 1 electroencephalographer, and 2 secretaries. There have usually been rehabilitation beds in an affiliated or in the same hospital.

The centres have dealt with only the cranial, and usually the spinal, wounds within the field allotted to them, but they have had to care also for the neurological maladies of the civilian populations of their proper districts—sometimes areas of many hundred square miles. Needless to say, this double burden of peace and war proved to be extremely

onerous, especially so because the Army had no neurosurgeons but those that it could get from civilian life. The armed services very rightly required all that they could get, and we have not failed them. Not only have the centres dealt with air-raid casualties, chiefly of civilians and much more rarely military, but they have played a major role in the treatment of soldiers too, for it has been their duty to help the Military. The Military have also had their own hospitals, but in neurosurgery the work has been widely shared with the EMS.

An idea of the work that these centres have done can be gained from the table below, which appertains to 6 centres and covers the first two years of the war.

TABLE
ANALYSIS OF 3045 ADMISSIONS
TO 6 NEUROSURGICAL CENTRES

Head injuries	1,509
Brain tumours	593
Brain abscesses	50
Epilepsy	125
Spinal tumours and injuries	219
Peripheral nerve lesions	102
Other conditions	447

By the middle of 1943, the total admissions had risen to 5,638, of which 46.8% were military personnel, the rest civilians. The reason why there were so few peripheral-nerve injuries was chiefly that such cases were collected into 3 other special centres designated for that purpose.¹ We have in Britain followed the pattern laid down in the last war whereby the nerve injuries have been in the hands of certain special orthopaedists, assisted by medical and sometimes surgical neurologists, because of the frequency with which fractures and severe soft-tissue injury complicate the cases. Only one of our special head centres was also a designated peripheral-nerve injury centre.

Nevertheless, some of the centres have done good work on uncomplicated peripheral-nerve injuries. Spinal injuries also are becoming more and more segregated into special centres, not always neurosurgical, and not orthopaedic either. Gun-shot injuries of the spine do not require immobilization in plaster, as the stability of the spine is not much endangered by a shell fragment. In this war, the fragmentation of the missiles has been such that small pieces of metal moving at high velocity have been the usual wounding agents. These do damage by penetration, or by traversing the body, but they do not very often shatter a spine. It has been a gratifying finding that by no means all of these wounds appear to result in total and lasting paraplegia. Recovery seems to be possible in about 25–30% of cases.

Pre-war Disposal of Head-injured

It was not the custom anywhere before the war for closed or blunt head injuries to be admitted only to neurosurgical centres. Neither Sir Victor Horsley nor Harvey Cushing had done so, indeed the latter, after his earliest years, took little interest in head injuries. To him, brain tumours were the cream of neurosurgical work. However, war imposes its own special necessities and, in relation to head injuries, not the least is the Army's requirement that the soldier should be returned to duty quickly, and in as high a category of physical fitness as possible. This is true in little less degree for the civilian, a man or woman more often than not engaged in some form of duty relating to the war effort. The handling of the head-injured by the general surgeon and practitioner in peace-time left much to be desired, too often the injury was followed by a long period of invalidism, mainly because the patient developed a neurosis. This was often due to conflict between his interpretation of his own symptoms and the stories told by different people, including his doctor and, not least, too-solicitous friends, families and chance contacts. A man who had not hitherto been important became so because of his head injury, for the first time he tasted local fame and found it an agreeable experience not too soon to be ended. All this was wrong, a radical change had to be brought about. It was done by collecting

¹ [The work of the peripheral-nerve injury centres has been described by Prof. H. J. Seddon in *BMB* 112.—Ed.]

all injured military personnel and such of the civilians as were engaged on special work into the special centres. We have not yet succeeded in reaching the total population for reasons that will be referred to later. We have this aim in view.

Notification and Present Disposal

The first essential was to find out how many head injuries there were. It was found that industrial head injuries are not very common, the majority occurring as a result of traffic accidents in town and countryside. The only means of tracing such injuries was by instituting notification, by which any case admitted to a hospital in a given district should be notified to the neurosurgical centre proper to its region. In this way it became possible, as in the case of an infectious fever, to follow the history of a head injury. Usually these patients were removed to the special head centre, not always immediately, but always within a week or two. With the help of Sir Francis Fraser, Director-General, EMS, and of Sir Claud Frankau, notification was imposed, not without some expostulation by the general surgeon. In one Region alone, 1,000 head injuries were thus notified, of which 178 had been caused by air-raids.

In head injuries there are two danger periods: first, the immediate danger to life, which rarely extends beyond a week; second, the danger to morale, which begins when a patient nominally leaves hospital. It was in this second period that the worst failures occurred. However, we were able by getting the patients into the special centres to help in the first period and to apply preventive measures to avoid the second. These measures have taken the form of reassurance and those orderly and pleasing forms of exercise that come under the headings of occupational therapy and rehabilitation. Moreover, a follow-up has been carried out so far as it has been possible, one centre sending reports to others if the subject normally lives in a different area. The Ministry of Labour has been of great help in finding suitable work for the injured, and the head-injured have been better and more sympathetically treated by the great industries than was the case in the days of peace.

Ability of Head-injured to Travel

It may be objected that, however desirable it is to get a person who has a head injury into a special centre, transportation will make the patient worse. We had, and still have, to contend with that dogma. It is true only of those who are so badly injured that they will not recover in any case, or of those who have had additional severe injuries elsewhere (e.g. fractures of the femur, ribs, or pelvis). It has been one of the outstanding lessons learned in this war that the head-injured can be moved without any decline in condition. On behalf of the Medical Research Council I undertook to report on the pulse-rate, blood-pressure and temperature of patients before and after a journey of 3 hours or so by road. Actually, it was very difficult to obtain sufficient information, but we were able to say that no significant alteration took place. This removed the greatest bar to transfer and segregation, for it is a matter of common knowledge that the head-injured are often most wisely taken to the hospital, great or small, nearest to the scene of the accident. Few doctors at first would take the responsibility for moving these patients from the first receiving hospital to a special centre, but experience taught them that it was not dangerous. Alternatively, a neurosurgeon from the nearest centre has visited the patient and given advice.

In this way the first danger-period, to which reference was made above, has been circumvented, while eventual transfer, if not in the first day or two, has done much to mitigate the dangers of the second period—that of unnecessary illness. When the battles began in Europe we were able to apply these lessons, and many hundreds with head wounds were flown home for their definitive treatment in conditions much better than the battle-field provides. We have learned thus that journeys of much longer duration than 2–3 hours are well tolerated, and that such journeys should be undertaken if better treatment can thereby be ensured.

Medical Research Council

A special committee of the Medical Research Council was set up to consider head injuries under the chairmanship of Professor E. D. Adrian, F.R.S. It has done much valuable

work, for the committee was made up not only of surgeons but of neurological physicians of the first rank and of psychiatrists as well. The committee published a glossary on the meaning of terms used in recording head injuries, giving definitions—for example of stupor and traumatic delirium—that have proved useful. Shortage of man-power has prevented us from undertaking experimental work that we should have wished to do. The improvised hospitals of the EMS were short of laboratory facilities of the right kind, and were often distant from the laboratories in which their staff had worked in peace time. Some laboratories were destroyed by bombs. But the committee was helpful in advising on grants-in-aid of work, in developing electroencephalography, and in defining the meaning of some of the chief states occasioned by trauma to the head.

Air-raid Casualties and Traffic Accidents

The number of head injuries caused by bombing proved to be much fewer than the pessimists had foretold. It may seem odd to the uninitiated, but it is possible to group together head injuries inflicted by motor-cars and by enemy bombs. There can of course be differences—marked differences—but often they are slight. Penetrating wounds of the head, with head-laceration by portions of bomb casing, were much less frequent than were blunt injuries caused by masonry when houses fell on their inmates. The proportion of severely injured to killed was almost equal statistically. The latest returns of casualties caused by bombing show that 59,792 were killed and 84,733 injured, i.e. the exact reverse of battle wounds. About one-third of those injured in air-raids had a head injury, but it was often of a minor kind. There was a high proportion of eye injuries. Glass, in small jewel-like fragments, propelled with great force by blast, proved to be a serious and dangerous form of missile. All of these facts we had to learn by experience. By comparison, forecasts of the nature of the gun-shot wounds of battle were a simple matter, for there has been no big change from expectation.

The congregation of all these injuries in the different centres allowed the neurosurgeon to see head injuries for the first time in the mass. His most immediate and striking impression, which experience confirmed, was that a very large proportion were not very serious. It is peculiar that, whenever the subject of head injuries comes up for discussion, we always think of them in exaggerated terms, picturing the worst cases. We must take warning and ensure that we do not confine our thoughts to such examples alone, because a planned system of treatment must take account of only a few severe cases in every hundred. The mortality of such congregations of head-injured is low, not more than 2–4%. It is well known that in some sets of figures in the literature the mortality is as high as 38%, while in many where the patients have been very well looked after it is 20% or a little less. The disparity between these percentages is due not so much to differences in surgical treatment as to differences in the material itself, to the fact that in some hospitals head injuries of all grades are admitted, while in others none but the worst are accepted. The differences are evidently caused, then, by the managerial side of the hospital which allots, as the case may be, very few or a large number of beds for head casualties.

We do well in speaking of the care of head injuries to use the word "management" rather than "treatment," for thus we emphasize the fact that the treatment of the patient in a bed is only a phase of a longer-sighted policy linked up with his rehabilitation and early return to duty, whatever that may be.

Method of Treatment of Closed Injuries

It should not be without interest to add a few lines about the trends that treatment has followed. With rare exceptions the American policy of dehydration as a routine treatment has been abandoned, in fact most of the Americans themselves gave it up some time ago. Dandy once said that he did not believe that anybody's life had ever been saved by it, and it is quite certain that death can be caused by abuse of this treatment. The trouble with the severer cases who remain unconscious for a long time—a state that some of us believe to be caused by a disturbance of the autonomic centres in the brain-stem or hypothalamus rather than in the cerebral cortex—is that they involuntarily dehydrate

themselves and become uraemic, unless they are fed by nasal intubation. It is care of this kind, the general nursing rather than skill in making holes in the patient's skull, which is of the greatest use to the greatest number. We have also abandoned the old-fashioned practice of nursing these patients on their backs with the head low. We keep the head high and nurse them on their sides or semi-prone. Every head injury is a potential cause for an intra- or extra-dural clot, the diagnosis of which may be more of a sport than an exact science.

It is very curious that ventriculography should have had so enthusiastic a reception, so wide a usage, and yet have been so little used for head injuries that I was only able to publish the first few readings on intraventricular pressure in head injuries as recently as 1942. They were not by any means high. Since that time, the use of pneumography has steadily grown. Sometimes a massive clot is discovered whilst the drill hole is being made. The use of inspection burr-holes has become a commonplace in treatment, but it is still the minority that require even that. Lumbar encephalography, too, has been used on the recovering cases, leading to the discovery of a puzzling post-traumatic internal hydrocephalus in a number of the severer injuries. Electroencephalography (EEG) has also become of great interest. Up to the present it is not of great immediate value in treatment, but that will change. The information gained has been an important help in giving a measured background to clinical judgment. It is quite likely that, with the use of portable EEG equipment, more practical information will be forthcoming in the future. All but one or two of the neurosurgical centres have used electroencephalography, and studies on it have been very greatly advanced by Grey Walter, Denis Williams,² and the Manchester Centre.

On the operative side, apart from the generalizations just made, extensive studies³ have been made on injuries of the frontal and ethmoidal sinus with and without cerebrospinal rhinorrhoea. Chemotherapy with sulphonamides and penicillin has done much to reduce their seriousness and to make operations upon them much safer than they were.

Information Derived from Lumbar Puncture

One lesson we have learned very fully is what to expect in the way of knowledge from lumbar puncture. The high pressures that many general surgeons have reported in large series of head injuries have not been confirmed by the more meticulous standards of the neurosurgeon. A struggling patient, or one whose breathing is embarrassed by the posture in which he has been placed, will always have a high pressure—a pressure bearing no relation to the neurological condition. The majority of unconscious patients have no more than a normal (80–100 mm water) or high normal (up to 180 mm) pressure. Only rarely is the pressure above 250 mm. We have come as the result of a very large experience not, I would say, to disregard the lumbar intrathecal pressure, but to relegate to it a lower degree of importance than it formerly had. It must be considered in relation to the general clinical picture. Even when it is high, it is no indication by itself that surgery is needed, it usually falls in 2–5 days to normal levels.

Of equal importance is the erythrocyte count of the cerebrospinal fluid (CSF). Very often there is no blood in the CSF in cases of concussion. This is an important fact for record in the notes of a patient who may in the future claim a disablement pension. For if there is no bleeding, one can be reasonably sure that no serious brain laceration has occurred. I think it likely, per contra, taking the observation from subarachnoid bleeding from aneurysms, that in those instances where there is very heavy contamination of the CSF with blood, an artery has been lacerated and, further, one with ready access to basal cisterns. There is experimental and clinical evidence for the view that this blood, even when large in amount, disappears at about the 5th or 6th day, and that its clearance is not very greatly assisted by lumbar-puncture drainage, although we usually employ it with reservations, being influenced by the patient's own statement as to whether he feels benefit from the punctures.

It has been objected that if blood is found on puncture the patient (if he knows of it), and the later examining doctor, are biased in favour of believing that post-traumatic symptoms, even long after, have an organic basis. This may be true, if it is, we should conclude that these examiners needed more knowledge of neurology. We should not accept the warning as an argument against finding out all that we can of the facts of a man's injury. It is true that lumbar-puncture findings are often incorrectly assessed, but it is more learning that we require, not less lumbar puncture.

The Return to Work

It has been said above that it is not difficult to get a head-injured back to duty if the case is handled throughout by someone who really knows his subject. There are many psychoneurotics in all populations and they are as much entitled to have a head injury as their more phlegmatic brethren. It is the psychoneurotics, especially the latent ones, whose emotional instability is unmasked by the temporary difficulties of their total situation, who form the greater proportion of those who by reason of headaches, vertigo, insomnia, and debility find it difficult to work day after day. All but the most refractory of these people can be returned to work in 6–8 weeks. Two factors have helped in earlier resumption of work: first, there have been more vacant posts in industry and secretarial work than there are people to fill them; second, the Ministry of Labour has been so helpful in suiting men to their work. We have seen the beginnings of something else too—the training by the same Ministry of disabled men to learn a new trade more suitable to their powers and present accomplishments. This speaks very well for the future. We hope to see this not only retained but expanded by Government planning after the war is ended.

The Future

We have reached a point when we can usefully enquire whether the plans that we made and put into action for the care of head-injured in war-time have been so beneficial that they should be prolonged and improved in time of peace. It will not, as I see it, be possible for every head injury to receive primary treatment in a neurosurgical centre. Not at least, in the immediate future. But that day might yet dawn. The difficulty is not with the great cities and large towns, but with the smaller places, and especially with country districts. Very many injuries occur in places far removed from highly-skilled help, and it says much for the recuperative powers of the brain that so many survive if they are placed in even the smallest hospital. The danger is that, the smaller the hospital, the longer it retains such a patient and the more unnecessary attentions he receives from its staff—too often leading him to believe that he is a wonderful man to have survived. There will perhaps always be some such instances even with the best of organizations.

However, there is something more than a hope, there is a very clear possibility, that under the new National Health Service, upon which legislation is expected, regionalized schemes for the care of designated categories of illnesses and accidents will be established. The plan would be to have an Accident Service that would include head injuries, with a neurosurgical consultant to advise. This at least would be the plan in the university city, or greatest industrial cities. In some centres it might be preferred to admit the head-injured to an enlarged neurosurgical centre. But for a population of, say, one million people, it would be necessary to add to the existing centre at least another 40 beds, with full rehabilitation facilities. We should expect head injuries in the smaller surrounding towns to be attended by general surgeons, who had undergone a training at their parent university centre in the methods of neurosurgery and in the meaning and interpretation of the clinical signs of head injuries, with a good background of neurophysiology. Surgeons without such knowledge should not be allowed to handle these cases. Furthermore, the general practitioner needs a great deal of instruction in the prognosis of the head-injured, his sense of values requires reformation. The worst thing that can happen, and it too frequently has happened, is for a patient to be sent home from a busy general hospital to the care of his own doctor, before he has been induced to walk about the ward and instructed about his

² [see article by Wing-Commander Denis Williams in this number—*BMB* 613]

³ [see also *BMB* 624]

injury and his prospects, not belittling their seriousness when they really are serious (as they rarely are), but not, on the other hand, giving him unjust cause for anxiety

Proper management can be achieved only by planning on a national basis. The experiences of the war have, I am con-

vinced, taught us that a planned scheme has great advantages for the injured, and it is one of the more important of the duties of the neurosurgeon in the future to ensure that head injuries are better cared for—not merely at the bedside, but in their convalescence—than they have been in the past

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THE ORGANIZATION FOR TREATMENT OF HEAD WOUNDS IN THE BRITISH ARMY

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Head wounds constitute between 5% and 10% of British battle casualties evacuated from the front line. Any discussion on organization for their treatment must be preceded by consideration of current methods of treatment, for this is really the root of the problem and must govern such matters as arrangements for personnel and their training, and questions of supply, establishment and siting of units

PART I. METHODS OF TREATMENT

Whether working in the forward area or at the base, British neurosurgeons are no longer satisfied with less than thorough excision of the wound and primary suture of the scalp. There are some brain wounds in which this cannot be done, but the proportion of unclosable wounds has diminished as we have learned to employ the methods of the plastic surgeons, and have gathered confidence in the ability of penicillin, and the tissues, to deal effectively with any bacteria that still remain after thorough excision of the wound

Preparations

A rapid neurological examination is carried out at all staging-posts on the way from the front line to the neurosurgical unit, and is repeated before operation. For convenience of rapid recording a special Head Injury Card is supplied (Fig. 1a, 1b) on which the essential features may be noted, one card for each separate examination. This information is of considerable value when it comes to assessing the operative priority of the case. Preliminary x-ray examination in two planes is essential, not only to give the surgeons an idea of the disposition of metal and bone fragments in the brain track, but also to unmask the brain wound with indriven bone fragments and metal lying beneath an apparently harmless-looking scalp wound.

The whole head must be shaved, otherwise inconspicuous wounds may be missed. This is a time-consuming operation which must be properly organized if the surgical team is to be efficient. All the operating-room assistants must be taught to shave heads, and to keep their razors sharp. The scalp is cleaned with 1% cetavlon (cetyl-tri-methyl-ammonium-bromide) which is not only antiseptic but also detergent and is remarkably effective in removing dried blood and dirt from the skin (Barnes, 1942). As it is not active against organisms of the coliform group, it should be followed by some other antiseptic, such as perchloride of mercury (1:1000).

Operation is performed under local or general anaesthesia, according to the condition of the patient and the preference of the individual surgeon. In comatose and semi-comatose patients the upper air-passages often contain much mucus, sometimes mixed with blood, in these it is advisable to aspirate the nasopharynx and the trachea before operation, in order to avoid chest complications, such as collapse of the lung, at a later stage. This work is done by the anaesthetist of the team, who is also responsible for giving blood and other fluids intravenously should they be required during operation. One anaesthetist can look after two operating tables with the assistance of a trained operating-room assistant.

Operative Methods for Penetrating Wounds

The methods of operation in an average case of brain wound up to 3 days old or older are illustrated in Fig. 3 and 4. The scalp and, in the temporal region, the temporal muscle, are widely excised. A burr hole is made in the intact skull alongside the skull opening and is enlarged until the dural

opening is freely exposed. The dura is conserved. The brain wound is now cleaned, with removal of pulped brain, old blood, dirt, hairs, fragments of bone, metal foreign bodies, etc. Particular attention is paid to the bone chips, brain abscess is apt to arise in cases in which clusters of bone chips have been left behind (Ascroft, 1943). Metal foreign bodies are removed if they are accessible, but tracks are not followed far beyond the zone of the indriven bone chips in search of small missiles (Fig. 3), because these may be hard to find and rarely give trouble at a later date. To clean brain tracks effectively it is essential to have continuous suction and good lighting. Special narrow illuminated retractors (Gillingham, 1944) are useful in cleaning deep tracks. After the surgical cleaning of the wound, the adjacent subdural space should be gently examined and any blood clot which is present should be removed. At this stage the brain should be slack, if it is not, the possibility that part of the track has not been thoroughly cleaned should be borne in mind and the track should be examined once more. It may be difficult to follow tracks across the deeper brain fissures (e.g., the Rolandic and Sylvian fissures), or to remove clot from the lateral ventricle in transventricular wounds, yet until this is done the brain may still bulge and the risk of subsequent complications remains higher than is necessary. Partial respiratory obstruction will cause the brain to bulge even after the track has been cleaned.

Throughout the operation careful haemostasis is of the utmost importance, and for this reason all British Army neurosurgical teams are equipped with surgical diathermy, silver clips, and fibrin foam (Ingraham & Bailey, 1944), in addition to the ordinary methods of haemostasis. Fortunately the tendency of excised brain tracks to bleed is not great, and general oozing usually subsides quickly when the cavity is lightly packed for a few minutes with cotton wool soaked in saline solution.

The dura is now closed, in the majority of cases, by suture if the opening is small, but otherwise with fibrin membrane (Ingraham & Bailey, 1944), or with autografts of temporal fascia or fascia lata. The scalp is closed in two layers, usually without drainage, where there has been great skin loss a rotation flap may be necessary (Fig. 5a, 5b). Before closure calcium-penicillin sulphamezathine powder (5,000 units of penicillin per g. of mixture) is insufflated into all parts of the wound, including the brain track, 1–2 g. of powder are used and this will maintain an effective antibacterial level of penicillin in the wound for about 24 hours. If the ventricle has been opened or a large cavity has been created by wound-excision (or if calcium penicillin is not available) sodium-penicillin solution (10,000 units in 5 cm.³ of saline) recently prepared by Seitz filtration may be poured into the wound before closure.

The methods of employing penicillin systemically and intrathecally and the indications for their use have been previously described (Cairns, 1944, Army Medical Department, 1945). A course of sulphadiazine (2 g. 4-hourly), or in humid tropical climates sulphamezathine (3 g. 4-hourly), is given by mouth for about 5 days. This chemotherapy can usually be applied without assay of the penicillin- or sulphonamide-content of the blood and cerebrospinal fluid, but if a patient is not making satisfactory progress, such estimations may be required. At its conclusion, the surgeon records his operation on a special form (Fig. 2a, 2b).

Special operative problems arise when a large venous sinus is injured, when a brain wound is associated with injury of the mastoid process or the accessory nasal sinuses in cere-

bellar wounds, and so on these cannot be dealt with in a paper of this nature. However, such cases do not call for equipment additional to that for operation on a typical vertex wound, such as has just been described. The disposal of this group is considered later.

Non-penetrating Wounds

In these cases, with the dura intact, the same principles of thorough wound-excision and primary suture, supported by chemotherapy, should obtain as in the treatment of penetrating wounds. When the operation is thoroughly performed, quick convalescence and early return to duty may be expected in most cases, though not in all. In gunshot wounds of the head with intact dura, unlike their counterparts due to road accidents, there may be considerable brain destruction beneath the site of the wound, as evidenced by the frequent presence of focal signs, e.g. monoplegia, hemianopia, and so forth. Recovery from these focal signs is usually complete, but may take several weeks.

Post-operative Nursing

Once a patient has recovered consciousness he rarely gives trouble, but in a ward for head wounds there is always a considerable number of unconscious, restless and incontinent patients, and the nursing of these requires more personnel than in most other wards. For a 24-hour service for 40 patients the minimum is 4 specially-trained nursing sisters, 4 V.A.D.¹ and 4 nursing orderlies, in addition, all ambulant patients should help by collecting stores and attending to the simple needs of their comrades who are still confined to bed, there could be no better way of beginning rehabilitation.² The unconscious patients must be turned frequently to avoid pressure-sores or chest complications, if there is much mucus in the upper air-passages, or difficulty of swallowing, it may be necessary to raise the foot of the bed on blocks. Fluids and sulphadiazine must often be administered by in-dwelling stomach-tube or intravenous drip. Examination of the cerebrospinal fluid from time to time provides useful information of the presence and progress of infection or bleeding.

Associated Wounds

In approximately one-third of the patients with head wounds there are wounds in other parts of the body. The sites most frequently damaged are the face and eyes, often by the same missile. Many wounds apparently limited to the eye are actually penetrating wounds of the brain, by way of the accessory nasal sinuses. Hence the neurosurgeon should work in close collaboration with the maxillo-facial, otorhinological, and ophthalmic surgeons. British Army neurosurgeons are expected to deal with the soft-tissue limb wounds

of their own cases, but in times of stress, when large numbers of head cases require operation, it is advisable to have a general surgeon attached to the head centre to deal with the limb wounds.

In a certain number of cases a head wound is associated with a penetrating abdominal wound or severe fracture of a limb. These are cases which cannot be moved for some days. They must be treated at casualty clearing station level.

Later Operative Treatment of Head Wounds

After the acute stage, when the immediate danger to life is past, reparative surgery is required in a certain number of cases. We hold the view that most patients with orbito-frontal wounds involving the dura of the anterior fossa should

have the dural openings repaired with fascia lata, otherwise there is risk that later they may develop meningitis (Fig 6).

All bony defects in the forehead, and most large ones further back, are repaired by plates of acrylic resin (Small & Graham, 1945, Beck, Russell, Small & Graham, 1945) or tantalum (Fig 7a, 7b, 8). We are relying more and more on our dental officers to prepare these plates.


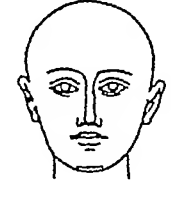
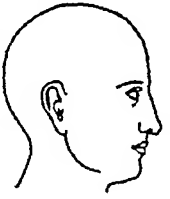
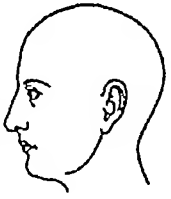
There are also a few cases of delayed brain abscess, but these have become rare as wound-excision and chemotherapy have improved.

Results of Treatment

With treatment on the lines indicated above, the following results have been obtained. In a series of 330 penetrating brain injuries from France and Belgium in the second part of 1944, admitted in the acute stage to a military hospital for head injuries, and subsequently observed for 2 to 6 months, brain abscess occurred in 17 cases and meningitis in 35, giving a total incidence of serious

infection of 15%.³ These cases were primarily operated on, either in Normandy or in Britain, usually within 72 hours of wounding, and the scalp was primarily closed in all but 11 cases. Of the total 34 deaths in the series there were 22 in which infection was the sole or predominant cause of death—which represents a death-rate from infection of 7%, or slightly lower if we exclude the patients who died from

ARMY FORM FOR RAPID RECORD OF NEUROLOGICAL STATE AFTER HEAD INJURY [0 5 diameter]



Army Form W 3118a.

HEAD INJURY CARD

For use in Field Ambulances, Casualty Clearing Stations and Stationary Hospitals.

At each station or Hospital a new card must be filled in and placed with the other cards in the patient's envelope — A.F.W.3118A.

NAME _____ No. _____
(BLOCK CAPITALS)

Rank _____ Unit _____

Date and time of injury _____

Date and time of examination _____

External injury? _____ If fracture seen? _____

Fractured? _____ Depressed? _____
(Site of external wounds to be marked on diagrams on back of this card)

NOTE: W 145187/73 3/50 612 A.F.W.14 C.1945

FIG 1a

All questions marked with interrogation mark to be answered with — + = Yes.
O = No

MENTAL STATE

Alert? Drowsy? Comatose?
Lucid? Confused?
Quiet? Excited? Irritable?

PUPILS

Dilated? Pin-point? Equal?
R. Larger? L. Larger?

WEAKNESS OR PARALYSIS?

Right limbs? Left limbs?

PULSE RATE _____ Fits? _____

RESPIRATION RATE _____

TREATMENT GIVEN

Morphia given _____ Dose _____
Sulphonamide given? _____
A.T.S. given? _____

PROGRESS UNDER OBSERVATION

Improved? Stationary? Worse?

REMARKS _____

Signature of M.O. _____

FIG 1b

¹ [V.A.D. is the abbreviation for Volunteer Aid Detachment, a voluntary auxiliary nursing service —Ed.]

² [If the ward also contains patients with spinal wounds and resulting paraplegia more nurses will be required.]

³ [For purposes of these estimates we define brain abscess and meningitis as follows. Brain abscess consists of any subcutaneous collection of pus which discharges spontaneously or is removed surgically, meningitis includes meningitis proved at necropsy, any case in which there were 1,000 or more polymorphs per mm.³ in a cerebrospinal fluid which was not bloody, any case of clinical meningitis with bacteria in the cerebrospinal fluid.]

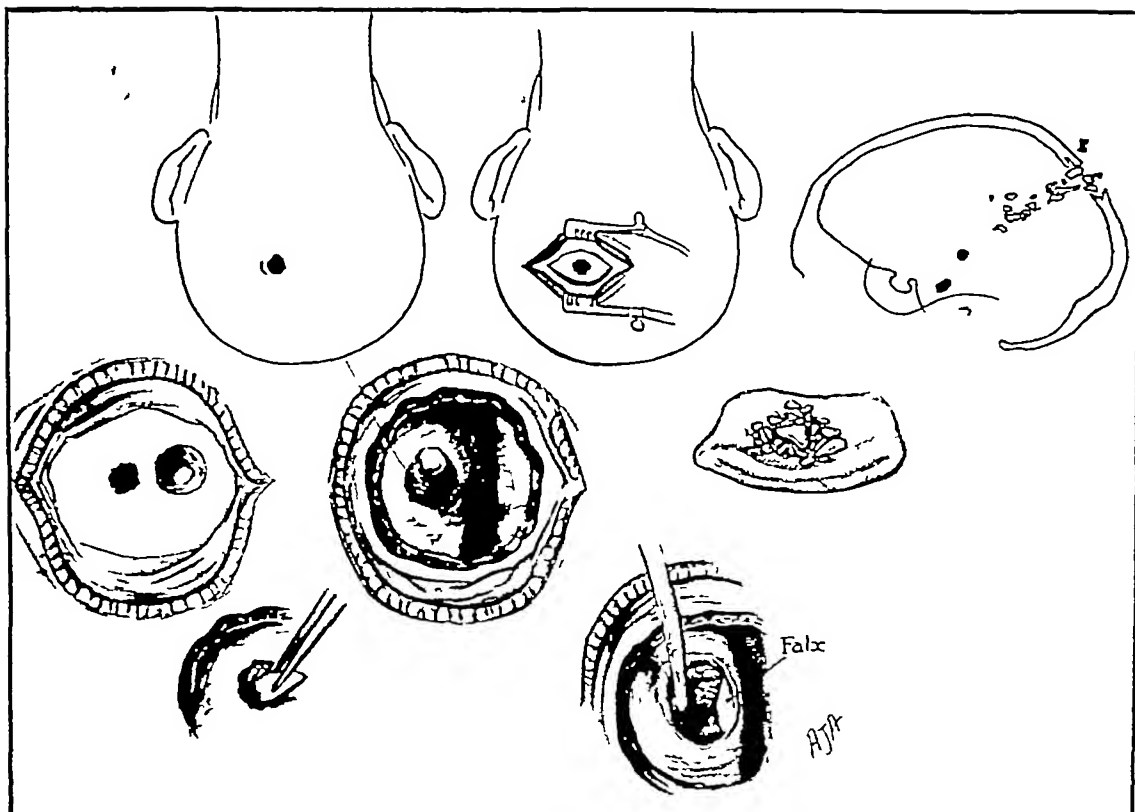


FIG 3 —Operative excision of small penetrating occipital wound

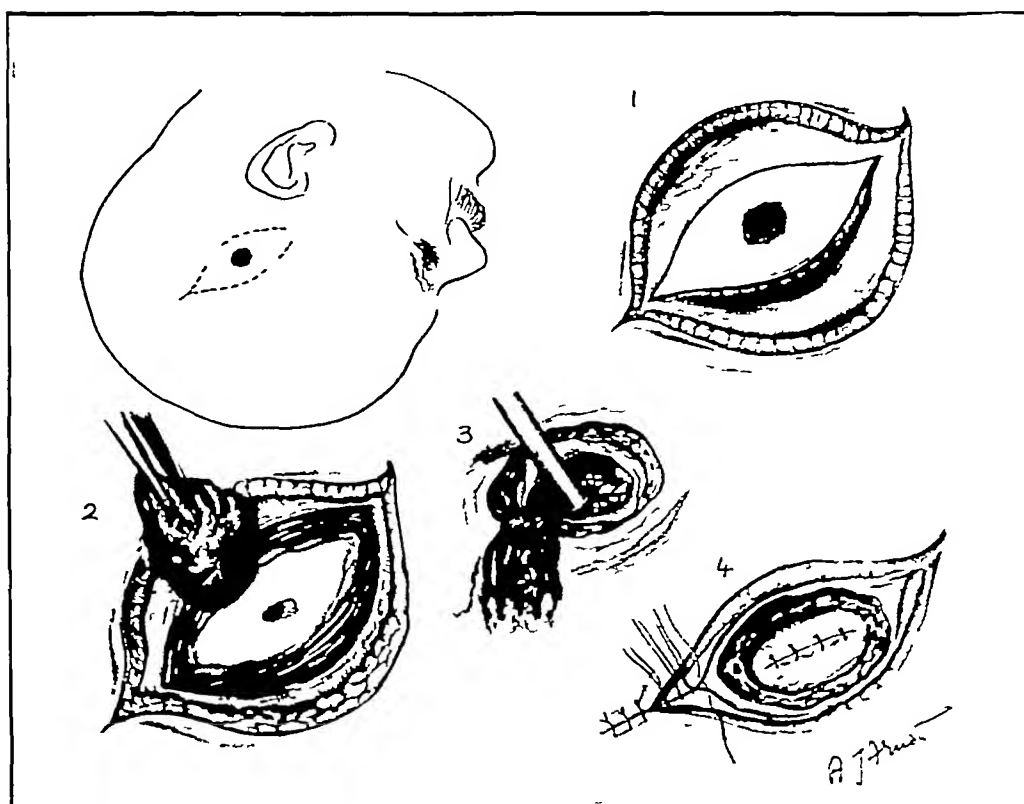


FIG 4 —Excision of left temporal wound, with closure of dura and of scalp



FIG 5a—Closure after excision of a large left temporal wound by means of a rotation flap



FIG 5b—Four weeks after operation

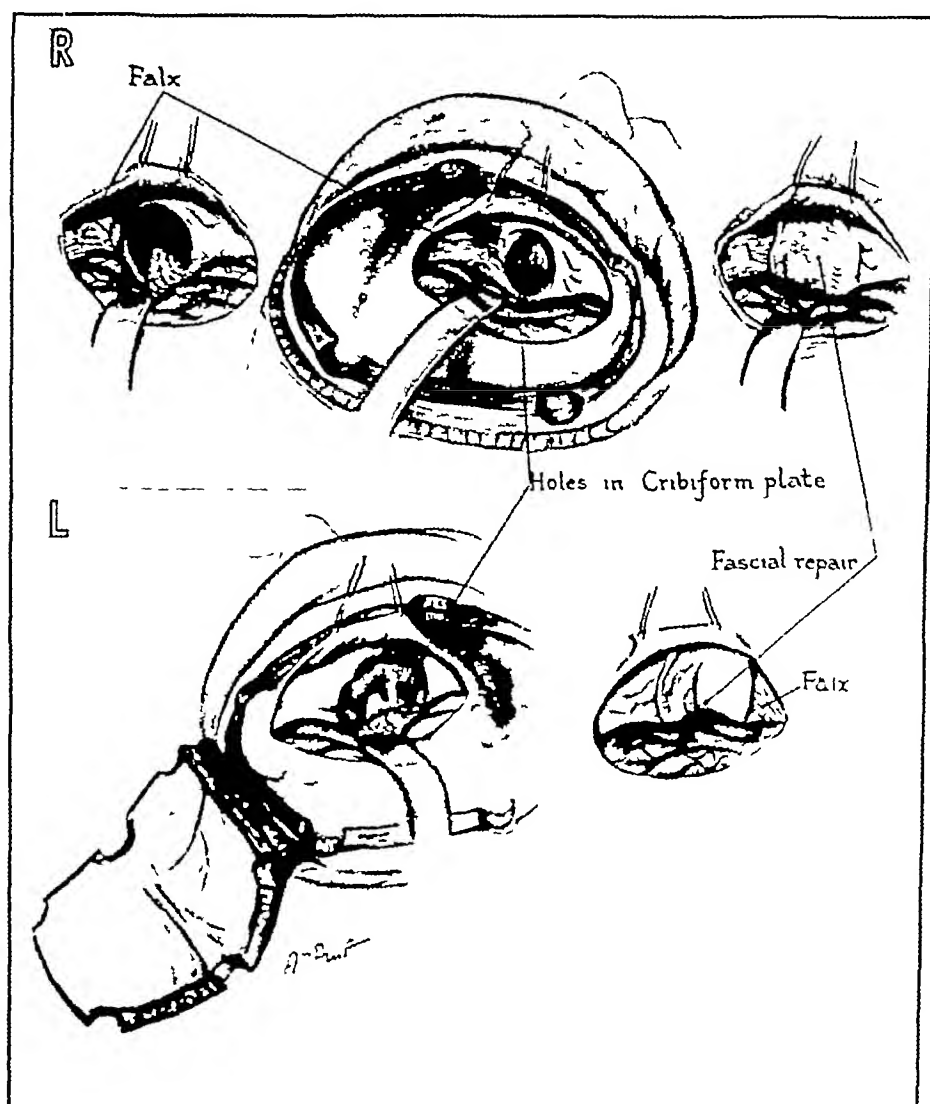


FIG 6—Bilateral fascial repair of torn dura over the cribriform plates after orbito-frontal gunshot wound

FIG 7 —Repair of defect of forehead and roof of orbit by tantalum plate

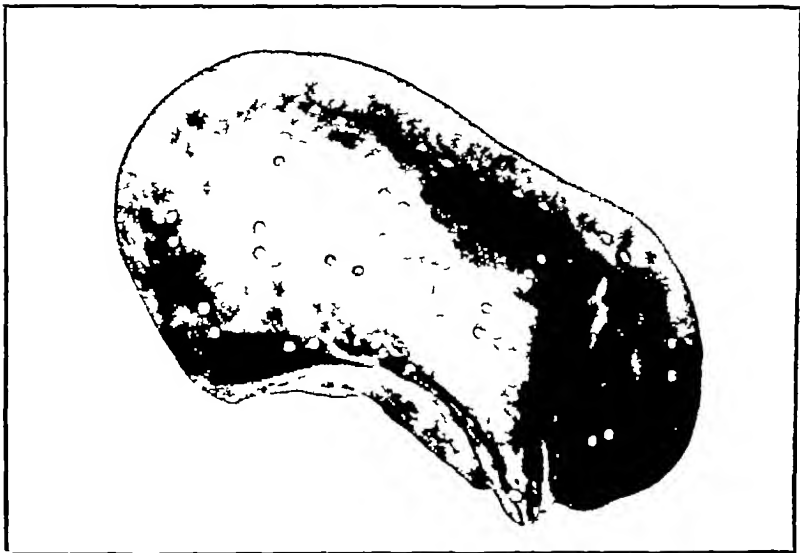
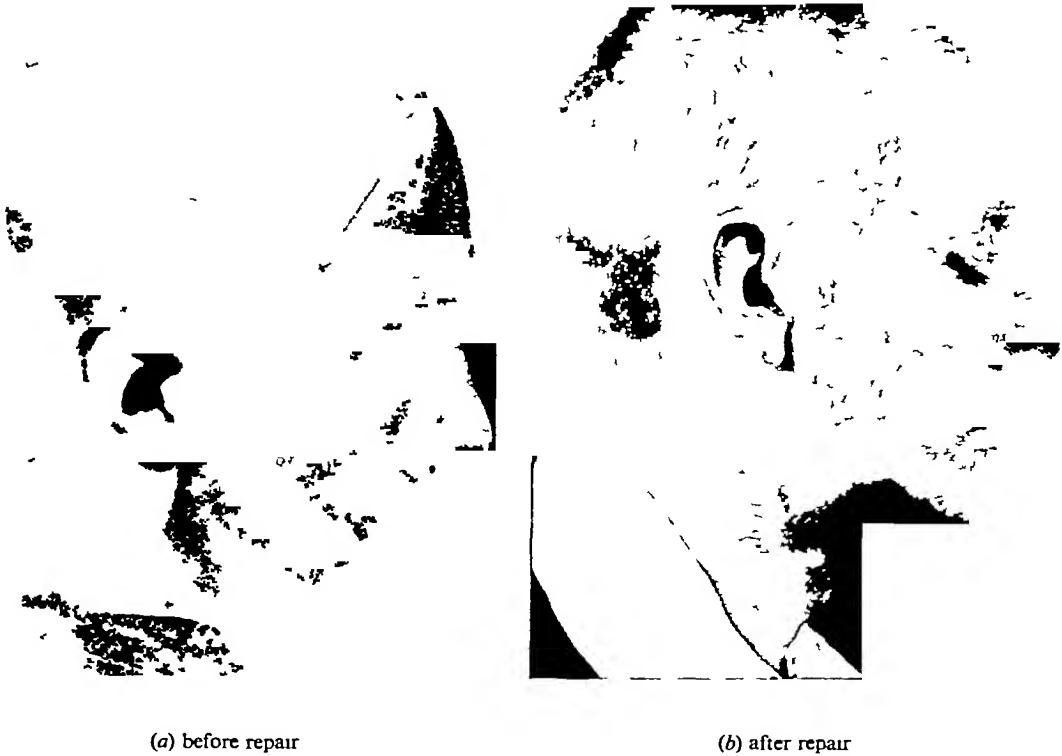


FIG 8 —Tantalum plate for repair of defect involving forehead temple, supra-orbital ridge, and roof of orbit



FIG 9—Equipment of mobile neurosurgical unit, showing from left to right distributor box and cables, drums for sterile linen, diathermy, portable light, bowl sterilizer and water sterilizer, with Primus stoves, instrument table, two operating tables, with anaesthetic apparatus between them, second instrument table. In the distance on the right are a stretcher on trestles, panniers and a vacuum pump for suction.

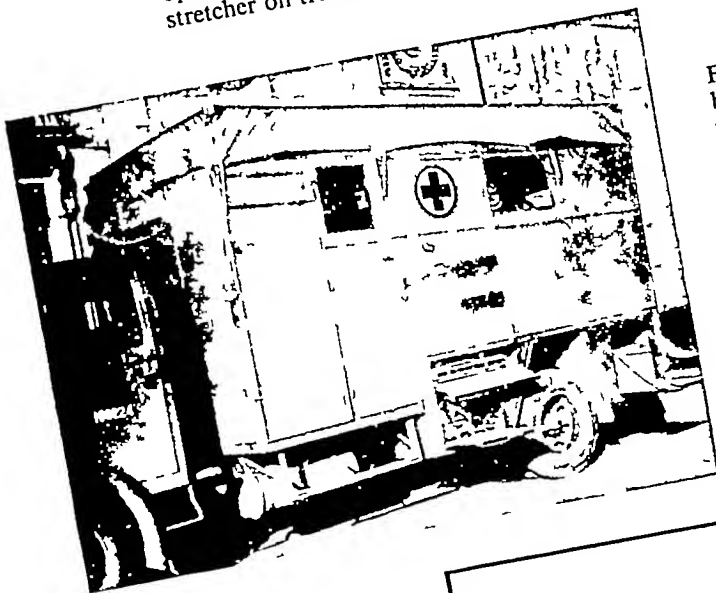


FIG 10—Truck for mobile neurosurgical unit. The body is divided into two compartments, of which the front one contains a petrol engine and dynamo, and the back one most of the operating equipment. Beneath the back compartment are seen small boxes into which are loaded the operating table and head rest.



FIG 11—Pent-house for operating theatre of mobile neurosurgical unit being set up in Western Desert.

the severity of their brain injuries before they had time to develop infection. Satisfactory healing (primary or near-primary healing) followed in 88% of the 370 cases, and brain fungus occurred in only 14 cases.

These figures may be contrasted with those of earlier series. Thus, in the last war Cushing (1918) operated on 133 brain wounds and 43 of these patients subsequently died of infection—31%. In this war Tönnis (1944) has reported 929 cases of brain wound of which 191 or 20.5% died of infection. In the Middle East in 1942 Ascroft (1943) had 75 cases of brain abscess in 292 cases of brain wound—i.e., approximately 25% as compared with our recent figure of 5%, in Ascroft's series the high incidence of abscess was largely associated with incomplete excision of brain wounds in the forward area. Three-quarters of the patients recovered after drainage of the abscess and removal of the remaining bone chips.

These series of cases are roughly comparable, and they show that in France in 1917 there was a high incidence of fatal infection, occurring very soon after wounding, in the

has been destroyed. An important contribution has been made by chemotherapy, in particular penicillin, and this is accompanied, not exactly by a clearer understanding of the principles of wound treatment, but rather by a clearer understanding of which principles are the important ones. Lastly, there is the contribution of the neurosurgical units working with our armies in the field. I will describe their part later, and will only say here that no important practical advances were made until head injuries were segregated within the first few days of wounding, and that did not take place until we had evacuation of wounded by air.

In the early stages of this war, neurosurgeons of most countries were apparently uncertain how far they could go with primary closure: the majority considered that wounds could be primarily closed if not older than 24 hours, and after that should be left open. There was incomplete understanding of the overriding importance of wound-excision, as is shown by the various recommendations regarding local antiseptics for the unexcised wound. With thorough excision and chemotherapy we have shown that the scalp

ARMY FORM FOR RAPID RECORD OF OPERATION ON HEAD WOUND [0.5 diameter]

Operation Card for Head Injuries

(For Distribution to Casualty Clearing Stations, Secondary and Tertiary Hospitals)

(Field Card No. W 2114a — to be filled in before operation)

No. _____ Name _____ Rank _____

Left _____ Right _____

Date of operation _____ Time (in hours) between injury and operation _____

Site of wound (enter on diagram) _____

Key findings: Fracture? _____ Foreign body? _____ Site of F.B.? _____

(Mark X-ray findings on diagram)

FIG 2a

Name (operator) _____

A. Is the patient employed? _____

Dura: Torn? _____ Intact? _____

Brain: Drained? _____ Lacerated? _____ Intact? _____

Infected? _____ By what organism? _____

Other findings: _____

OPERATIVE TREATMENT —

What foreign bodies removed? _____

Drainage? _____

Signature _____

FIG 2b

Middle East in 1942 there was a high incidence of brain abscess, but most of the cases were saved by subsequent operation. In the 1944 series from Normandy the incidence of fatal infection showed a further reduction and the primary healing rate was remarkably high. In the German Army the death rate from infection still appears to be high.

In the non-penetrating wounds (i.e., with the dura intact) the mortality is less than 1%, and the rate of return to duty is high. In penetrating wounds of the brain the rate of return to duty is naturally lower, figures on this question are of little value, for they vary with the varying needs of the Army for men for duty at the base. It is the exception that a soldier with a brain wound will subsequently fight well as a front-line soldier, though he may do well in steadier work involving less strain.

To what can the improved results be ascribed? There is no doubt that the advances of neurosurgery between the wars have contributed much—such technical improvements as continuous suction, diathermy and fibrin foam for haemostasis, a better knowledge of the means of controlling intracranial pressure and of nursing the unconscious patient. Much has also been learned from the plastic surgeons concerning the methods of closing the scalp in cases where scalp

can be primarily closed in the vast majority of wounds of up to 72 hours, and often in older wounds.

PART II ORGANIZATION

In Britain

On matters relating to head injuries of all types the Director-General of the Army Medical Services is advised by a consultant neurosurgeon⁴ and a consultant neurologist (Brigadier G. Riddoch). Each of these consultants looks after his own specialist personnel, over matters of common interest there is the closest collaboration, and there has never been any need to define formally their separate functions.

At the outbreak of war there was set up in Oxford a military hospital of 300 beds for head injuries and other lesions of the nervous system. In the pre-war planning it was assumed that in a modern mechanised army there would be a large number of head injuries from road accidents and the like, as well as from battle wounds, and the hospital has, in fact, been continuously and fully employed in quiet times with closed head injuries and at other times with gunshot wounds. It has returned large numbers of men to duty.

⁴ [The author of this paper—Ed.]

has acted as a training centre for neurosurgeons and neurologists, and as the parent unit for the mobile neurosurgical units proceeding overseas, and by its investigations it has influenced considerably the treatment of head injuries in the British Army. The hospital has also been closely associated with the R A F the consultant neurologist to the R A F (Air Vice-Marshal C P Symonds) was largely concerned with the Army representatives in the pre-war planning of the hospital and since then with its work, a varying proportion of the patients, at times as high as 25 %, have been R A F personnel. The hospital has also treated special cases from the Royal Navy, Merchant Navy, Allied Armies, etc. Between February, 1940 and 31st December, 1944, the hospital has treated over 10,000 patients.

Considerable advantage has resulted from contacts with the adjacent university (Oxford), particularly in relation to medical research. It would take too long to describe the many ways in which the pre-clinical and clinical departments of the university have co-operated, by providing laboratory accommodation, technical assistance, supplementary researches, and above all by making available the results of their own research work for immediate application. The Medical Research Council has also assisted with an annual grant for the keeping of clinical records and follow-up notes.

In the adjacent countryside there are two British Red Cross convalescent hospitals devoted solely to rehabilitation of head-injury patients from the military hospital and receiving regular weekly visits from the staff of this parent hospital. One hospital takes the patients who are likely to be fit to return to duty within a reasonable time, while the other specializes in patients with severe brain injury who are unfit for further military service—aphasics, hemiplegics, and the like, who must be trained for return to civil life. A remarkable degree of recovery of function is often seen in these patients in the first few months after injury.

This military hospital and its adjacent convalescent hospitals can deal with only a portion of the Army head injuries, its work is co-ordinated with that in similar centres in other parts of the country which are under the Canadian Army, and the Emergency Medical Services of the Ministry of Health and the Secretary of State for Scotland.

Overseas

With the forces overseas there have been since 1940 mobile neurosurgical units with their own establishment and, later, within the establishment of a few general hospitals, more static head centres. In each of these units and centres there are neurosurgical and neurological specialists. Their work has been the particular concern of the consultant neurologist, or the neurosurgical or neurological adviser, of the Force, working in collaboration with the consulting surgeon. Experience has shown that such continuous supervision of the neurosurgical units by someone who specializes in disorders of the central nervous system is an important factor in promoting their efficiency.

The first mobile neurosurgical unit was mobilized early in 1940, and since then similar units have served in all the major campaigns. Each unit has a neurosurgeon, a neurologist, an anaesthetist, and two general-duty officers, together with specially-trained nursing sisters and other ranks. The unit carries equipment for operating, and for sterilizing bowls and instruments, it relies on its parent unit for the housing, nursing and feeding of its patients, and for sterilization of its linen. These units have their own transport and are truly mobile (Fig 10). They carry a petrol engine and generator which supply power for theatre lighting, surgical diathermy, a motor suction pump, operating-table heaters and instrument sterilizers. Each unit is equipped to work two operating tables (Fig 9) and can carry sufficient material for several hundred neurosurgical operations.

The first mobile neurosurgical unit arrived in France only a few days before the Germans invaded Belgium and Holland, and was attached to a casualty clearing station (CCS) where, after evacuation of its nursing sisters, it was captured while in surgical charge of some 800 wounded. Subsequently in Germany the neurosurgeon of the unit, Major W R Henderson, has done work of outstanding merit, to judge from the accounts of successive batches of repatriated prisoners of war. Some 18 months later, at Benghazi, another neurosurgical unit was confronted with risk of capture, but by that time the mobile function of these units was thoroughly understood. The Commanding Officer,

Major P B Ascroft, was able to continue operating until within a few hours of the re-entry of Benghazi by the Germans, and then the unit withdrew with all its vehicles and equipment (*Journal of the Royal Army Medical Corps*, 1942).

In this particular tour of duty with the Eighth Army in the Western Desert, from 18th November, 1941 to 1st February, 1942, Ascroft's unit learned much about mobile surgery in the desert. This was the time of the battles of Sidi Rezegh and the advance to, and subsequent retirement from, the borders of Tripolitania. In 10 weeks the unit worked with various CCS in some eight locations ranging from the Libyan border to Benghazi. Their operating theatre was a pent-house, 38 feet by 30 feet, erected around a 3-ton Bedford lorry (Fig 11). The unit treated over 300 recently-wounded men, of whom, however, less than 10 % had head wounds, the rest being general surgical cases. As a result of this experience the unit was subsequently moved to the base, where head cases could be segregated, but this tour of duty in the desert, though not neurosurgical, had been valuable in testing equipment and developing the technique of desert surgery. This was the period of experimentation when, under Major-General D C Monro, the modern mobile forward surgery of the Eighth Army, and for that matter of the British Army, was put on a firm foundation.

The battle of Alamein, late in 1942, brought the first large-scale segregation of head wounds. Patients were flown to Cairo, where Ascroft's unit admitted some 250 cases within a period of 14 days. Some of these cases had already been operated on in the forward area, while others arrived untouched, comparison of the two groups established the fact that it was better to delay primary operative treatment for 2 or 3 days in order to get the case to the neurosurgical centre than for a surgeon unused to handling brain wounds to do a partial wound-excision within a few hours of wounding (Ascroft, 1943).

After Alamein the fighting moved rapidly west. The lines of communication became favourable for early segregation, and another mobile neurosurgical unit was sited with a forward CCS. From Alamein to Tunis this unit, under the command of Major K C Eden, whose untimely death from poliomyelitis some months later was such a grievous loss to the Army and to surgery, dealt with over 300 head wounds, mostly within 24 hours of wounding (Eden, 1943). When a forward base was established at Tripoli the unit was split into an advance section and a rear section, the one with the most forward CCS, and the other at Tripoli. In this way the neurosurgical net was so spread that practically all the head wounds were treated by the neurosurgeons. During the heaviest rush of casualties the work of the forward team was lightened, as they could transfer cases to the rear section by air, the milder cases without operation and the severe cases soon after operation. Contrary to the teaching of the last war, these patients were found to travel well by air.

Since the Tunisian battles it has been a common practice to split the mobile neurosurgical unit into forward and rear sections. The original basic equipment suffices, with certain additions such as extra diathermy and suction, but the personnel are rather thinly spread, and for this reason the establishment of the units has been recently reconsidered.

The pioneer work of Ascroft and Eden and their teams, along with that of Schorstein's unit in North Africa, firmly established the position and functions of mobile neurosurgical units and assured them a good place in the order of battle of our armies overseas.

The Italian campaign of 1943-44 brought a new development—the methodical association of the neurosurgical units with the more recently formed maxillo-facial and ophthalmological units. Not only was this a great advantage in the treatment of the many cases of head wounds involving also the face and eyes, it was also a great convenience to forward units responsible for sorting and evacuating cases. This trinity is now a firmly-established institution in most of our armies, and the time is probably not far distant when it will be joined by an otorhinolaryngologist. Such a quadruplicity could undertake to treat expertly any wound above the clavicle.

Now I come to the Normandy campaign, where a British unit under Major J M Small and a Canadian unit under Major W S Keith dealt with large numbers of cases. My remarks are limited to the work of the British unit. In Normandy for a time the volume of work exceeded anything which our units had before encountered, and as many as

50 patients might be awaiting treatment at any one time. Fortunately air transport became available soon after the beginning of the campaign, and about half the cases were evacuated without operation to neurosurgical centres in Britain, the great majority arriving within 48 hours, but some on the very day of being wounded, the remainder were operated on by the neurosurgical unit in Normandy.

The policy of early evacuation of unoperated head cases requires the most careful sorting of the patients, and this process of deciding who is fit for air evacuation and who must remain and be operated on forthwith in a graded order of priority is usually the function of the medical neurologists attached to the neurosurgical units. It is a testing task which may often have to be done without the aid of x-ray studies, and calls for clinical skill of a special kind, most easily acquired by those neurologists who have previously had some training in neurosurgery. Of the 2,000 and more head cases evacuated from Normandy, not all from choice, during the heaviest rush of battle casualties, only 3 died in transit.

As the pressure of work continued to be so great, it was not possible for the units in France to hold their cases for any length of time, and most patients were sent to Britain by air 1-3 days after they had been operated on in France. On the whole this was satisfactory, but a few patients arrived with massive collapse of the lungs, or developed this soon after arrival, and the question was raised whether they were not being evacuated too soon after operation. Enquiry showed, however, that chest and other complications were infrequent and that they were limited to patients inert from coma or hemiplegia, both pre-operative and post-operative. Of 1,000 head cases evacuated from Normandy by air, 16 developed collapse of the lung, and of these 7 had had no operation. All were inert patients, no restless patient developed this sequel. It was concluded that this complication was due not to a recent operation, but to the fact that the patient who is inert lies too long in one position on the stretcher. Clearly, all types of inert patient require frequent slight alterations of position during transit, and instructions have been issued accordingly.

During August 1944 in Normandy, an advance section of the neurosurgical unit worked at CCS level, and one-third of its patients had head injuries combined with a severe injury elsewhere, such as a penetrating abdominal wound or a limb wound involving bones. These were patients who could not be moved and for whom segregation, even in the forward area, is usually impossible. It was only the peculiarly favourable conditions for the clearance of wounded in Normandy which revealed the importance of this problem, and at the same time gave further support for the view which has been held for some time by our neurosurgical units—that a high mortality-rate, if it means anything at all, indicates good clearance of wounded from the forward area, whereas a low mortality-rate after early operation for brain wounds certainly means that evacuation of wounded from the fighting area and their subsequent segregation have not attained the highest standards.

In Assam during the Burma-Assam campaign of 1944, one of our neurosurgical units under the command of Major R. T. Johnson treated some 350 gunshot wounds of the head, mostly grenade- and bullet-wounds. His unit was first at Imphal and later moved by air, together with 18 ill patients, to Comilla, where it was better placed to collect patients from the Arakan front, as well as from the Chindwin valley and Imphal. In the mountainous jungle of the Assam-Burma border the lines of communication were difficult, wounded had to be brought along shallow rivers in native boats or outboard motor-boats, over hill-tracks by mule, and then along tortuous single-track roads. The majority of the patients did not reach the head centre until the 4th day or later after wounding, though the wounded from the fighting in the Imphal box reached Comilla in under 48 hours. Operating was done at night, but even then in such great heat and humidity that very few patients could tolerate operations under local anaesthesia—it was more than they could bear to lie under the operating towels for an hour without moving. "Even to be in the theatre at all and free to move about," writes Major Johnson, "was productive of the greatest discomfort. Later when the monsoon broke it became possible to use local anaesthetics more and more. Dust and flies abounded. Of 167 penetrating wounds, 30% showed frank pus on admission and a further 10% showed it later. In the climate

of Comilla it was impossible to close wounds more than 4-5 days old, though it could be done at Imphal. On the Burma front there were many special problems e.g. whether a Sikh with a scalp wound would be allowed to return to his regiment without disgrace and degradation if his scalp had been shaved, how to restrain the African native from removing his head bandage and the tube in his brain abscess in preparation for a morning dip in the water tank, how to prevent the Indian from wriggling out of his plaster bandage, how to administer sulphonamides in a climate where there is so much sweating that a large proportion of patients on full doses of sulphadiazine will rapidly develop dysuria, and if they are Gurkhas or Africans will not complain of it. All questions of supply were especially difficult.

The Human Factor

Before leaving the neurosurgical units, something must be said on the question of fitting small specialized units into the general framework of the Army Medical Services. There are undoubted advantages in a small unit: the unit is flexible and can be quickly adapted to the exigencies of war, a fine team-spirit quickly develops, not only the commanding officer, but all the medical officers, rapidly learn the military side of their work, and with considerable zest, they take a keen and critical interest in tactics, especially as concerns the siting of their own unit, all ranks become competent in such technical matters as the handling of their surgical equipment, generators, vehicles, and so forth. In no campaign have our units failed to rise magnificently to their opportunities. At the same time, there are certain disadvantages in the small specialized unit, from the point of view of central organization they must be something of a nuisance, though I would like to say here that no hint of this has ever been displayed at the War Office, and the willing and efficient service given to the units by all branches of the Army Medical Department, and by consultants and administrators overseas, has contributed largely to their success. In the field, the neurosurgical units move from one parent unit to another, which may be a CCS or general hospital of 200 beds or more. Each of these is expected to supply operating theatres, ward space, and help of a general kind, and the requirements may sometimes put considerable strain on the parent unit. There is now a considerable number of small units to be looked after in the same way as neurosurgical units, and parent units on the whole clearly recognize their responsibilities in this direction.

Neurosurgical Training for General Surgeons

In most campaigns the mobile neurosurgical units have dealt with a high proportion of the head wounds (in Normandy well over 90%). However, it is not always possible to get the head cases to the neurosurgical units in time for primary surgical treatment. There are not enough, and never could be enough neurosurgical units to staff the whole forward area, and there are patients with multiple wounds—for example one with a head wound and a penetrating abdominal wound—who cannot be moved for some days. In addition, in some campaigns it has not been possible to segregate even the uncomplicated cases, e.g., in the 1940 battle of France, and the Western Desert battles before Alamein. Recognizing that in some battles, particularly in the early phase of an operation, this state of affairs may be inevitable, the War Office and the civilian neurosurgeons have made several attempts to develop training schemes in the United Kingdom, by which young general surgeons designated for surgery in the forward area could receive training in head-injury work at civilian and Army neurosurgical centres. For a variety of reasons these attempts at training in the United Kingdom have never been a success. Meanwhile, however, in the Commands overseas, first in the Middle East and later in North-west Europe, a more effective type of training has been developed. During a rest period out of the line the surgeon of the Field Surgical Unit is attached with his team to a nearby neurosurgical unit for a period of about 3 weeks. The surgeon and his team take part in primary operations on head wounds and quickly learn to handle neurosurgical tools and to do a workmanlike excision and primary suture of the average brain wound. So far this scheme of training overseas has functioned only in a small way, but it has proved so satisfactory that the War Office has now arranged for its more systematic application in distant theatres of war and

hopes eventually to have neurosurgically-trained and equipped Field Surgical Units with every Army Corps. These units will continue to do general surgery and in addition will operate on such patients with head wounds as cannot be evacuated promptly to the neurosurgical units. The majority of the head wounds will continue to be dealt with, whenever possible, by the mobile neurosurgical units.

Conclusion

Thanks mainly to air evacuation and chemotherapy, it has now been established beyond question that it is feasible in most battles to put into effect the rule that the primary brain operation should be definitive, final—a thorough excision of the wound and primary two-layer closure of the scalp, with or without closure of the dura. This operation is worth waiting for, and in most brain wounds can be delayed for up to 72 hours. Speaking generally, the greater the distance behind the lines, the greater the facilities for doing this operation, and the more time at the disposal of the surgeon. But we must still prepare for the same type of operative treatment of brain wounds at three levels.

i At the level of the most advanced operating teams, operations must be done on those cases which cannot be moved, either because of multiple injuries or because of absence of an air-strip at the beginning of an invasion, etc. Here the operation may be undertaken, according to circumstances, by a neurosurgically-trained surgeon of a Field Surgical

Unit or by the advance section of a mobile neurosurgical unit.

ii At the overseas base (forward or rear). At this level the head cases should be segregated in a neurosurgical unit. The policy in regard to head wounds varies considerably according to circumstances: sometimes the most severe cases are operated on at this level and the rest are evacuated to units further back or to the United Kingdom (as in the early days of the Normandy campaign), at other times all cases are operated on and all but the most severe are subsequently held and are returned quickly to duty without going down the line (as in the battle of the Gothic Line in Italy).

iii In the United Kingdom. Always the guiding policy should be to send the severely wounded as far back as possible for operation. It is perhaps not yet sufficiently realized what can be done in this way with air transport. During the Salerno battles of 1943, head cases were flown to Tripoli for primary operation. The neurosurgical unit in Tripoli was in process of moving to Sicily, and a day or so after this move was complete some 12 head cases arrived in Tripoli by air and there was no neurosurgeon there to treat them. They were put in a plane and flown 1,000 miles to Cairo, where they received expert neurosurgical treatment after a delay of only 12 hours.

There is little doubt that the most important contribution which could at present be made to the medical organization for treatment of head wounds is improvement in the facilities for air evacuation.

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⁵ [BMB 638]

⁶ [BMB 641]

PROGNOSIS IN CLOSED HEAD INJURIES

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A closed head injury may be defined as one in which the force, however applied, has not involved penetration of the dura mater. This definition would logically include non-penetrating gunshot wounds, but these have special features and need separate consideration, and this review will be devoted to closed injuries caused by the impact of blunt objects.

Historical

The effects of closed head injuries were little studied before the last 25 years except by surgeons, who were preoccupied first with the significance of fracture of the skull, which is now recognized as usually of minor importance, and later with the serious but rare occurrence of cerebral compression by meningeal haemorrhage. Although immediate loss of consciousness following the injury was assumed to be due to cerebral concussion, it was not suspected that many of the ill-defined symptoms of the later stages might be due to persistent brain injury. In a few cases, it is true, frank mental disorder or undoubted personality-change attracted the attention of psychiatrists, and Meyer (1904) contributed the first important study of this aspect, followed many years later by Strecker & Ebaugh (1924), who observed behaviour disorder in children.

Psychological disorder of minor degree, however, was widely regarded as "neurasthenic" until Trotter (1925), from his examination of patients with closed injuries of varying severity, concluded that many symptoms which in the past had been regarded as neurotic were in fact due to minor injuries of the brain. There followed papers by neurologists (Symonds, 1928, 1932, Russell, 1932) concerned with the assessment of the extent and severity of the injury in the

early, as well as in the later stages, and especially with prognosis. In the past 12 years it has been generally recognized that, although in most cases of closed head injury surgical attention is necessary for the scalp, the major problem is the assessment of brain injury by neuro-psychiatric methods. There has thus arisen the opportunity for many valuable studies in which the problem of prognosis has been considered. The war has provided an increase of clinical material and an additional interest in prognosis owing to the demand for man-power.

Prognosis in the Acute Stage

The acute stage of illness resulting from a closed head injury will be defined as lasting until the patient has recovered clear consciousness, that is to say when he is able to think clearly and with customary rapidity, and to perceive, respond to, and remember current stimuli, and is normally orientated (Medical Research Council, 1941). Alternatively, in a patient suffering from the effects of a closed injury without disturbance of consciousness, the acute stage may be arbitrarily limited to the first 24 hours. If there is disturbance of consciousness, the first task of the physician will be to record its depth. The gradations¹ recommended by the Brain Injuries Committee of the Medical Research Council (1941) have practical value. Coma persisting longer than a few hours, or semi-coma (defined as a state in which psychologically understandable responses are elicited only by painful

¹ [These gradations are: coma, semicoma, confusion, delirium, traumatic stupor, traumatic automatism, concussion, traumatic dementia, traumatic intellectual impairment, traumatic personality disorder, malingering, hysteria, insight, judgment, comprehension, amnesia.]

or other disagreeable stimuli) lasting more than a day or two, give cause for anxiety as to life

When coma persists from the moment of the injury over a period of several hours and is associated with evidence of shock—a weak rapid pulse, cold moist skin, and low temperature—death usually follows quickly and is found to have been due to extensive laceration of the brain, which, though most often associated with severe skull fracture, may occur without this, or indeed without laceration of the scalp. In such cases the pupils are usually widely dilated and inactive, and the limbs flaccid. In patients who survive the stage of shock, but remain in a state of coma or semi-coma the prognosis for life may remain doubtful during the first 48 hours. After this period the mortality-rate is low in cases uncomplicated by meningeal haemorrhage or meningitis.

In large consecutive series of accidental injuries admitted to hospital (and therefore not including cases of minor injury) Jefferson (1933) found a mortality of 23% and Munro (1934) 17%. These figures, however, include cases of compound fracture and meningeal haemorrhage. In a series of 405 cases admitted under his own care, excluding those with meningeal haemorrhage and compound fracture, Munro found a mortality of 10.3%. In 152 fatal cases in Jefferson's series in which accurate information was available, death occurred within 48 hours of the injury in 109. It has been noted (Russell, 1932; Woodhall, 1936; Davis, 1938) that during this critical phase, temperature, pulse and respiration considered in relation to the state of consciousness are of prognostic value. Thus, unless there is a steady improvement in the level of consciousness, a subnormal temperature and rapid pulse are of bad omen, so also is hyperpyrexia. Rapid and irregular respiration is also a bad prognostic sign. When there has been cause for anxiety, a slowing and hardening of the pulse wave is to be welcomed. Most important of all, however, is improvement in the level of consciousness. Once the patient can be roused to answer questions he is usually out of danger.

In the severe cases after the period of greatest danger to life is over, and in the milder cases, the state of consciousness still needs to be watched from day to day for evidence of that progressive deterioration which is usually the first sign of cerebral compression from extradural or subdural haemorrhage. Leakage of cerebrospinal fluid from nose or ear indicates the danger of meningitis which, until the advent of modern antibacterial treatment, was a complication which usually ended fatally. In elderly patients a rise of temperature and respiration-rate during the period of confusion may herald a fatal issue from pneumonia, though the cerebral symptoms have been improving.

Neurological examination in the early stages may reveal local damage to the brain or cranial nerves of a degree which indicates the likelihood of persistent disability. When the patient becomes responsive, investigation can be carried further. Paterson (1944) has noted in the confusional state outstanding disturbance of special functions—dysphasia, visual agnosia, acalculia, and constructional apraxia for example—which being then at their worst and most easily observed, are useful clues for the interpretation of any persistent psychological disorder. He has also (Paterson, 1942) observed during the confusional state abnormal emotional responses, tending to fall into two groups—excessive fear and anxiety on the one hand, and euphoria and aggression on the other—which he believes to be the result of organic cerebral damage, and which indicate the possibility of personality disorder in the later stages.

Special investigations seldom yield information of prognostic value. The x-ray picture may occasionally reveal some important feature, such as a fracture involving the nasal sinuses, or an intracranial aerocele. The cerebrospinal fluid pressure has not been shown to bear any constant relation to the mental state or to the subsequent course of the illness (Turner, 1941; Paterson, 1943). Paterson (1943), however, observed a higher incidence of blood in the cerebrospinal fluid of cases with a long post-traumatic amnesia, and as the latter has prognostic significance it is possible that the absence of blood in the early stages may be a relatively good prognostic feature. The changes shown by the electroencephalogram (Williams, 1941a) are related to the state of consciousness and give no indication in this stage of the ultimate prognosis unless they reveal an area of local damage.

When there has been no initial disturbance of consciousness, it is of course comparatively easy to discover the

presence of a local cerebral contusion, if this has involved any of the highly specialized areas—for example those concerned with speech or vision—or damage to the cranial nerves. In the absence of such signs the patient's subjective symptoms will furnish a guide. If there are no symptoms at this stage it is probable that none will develop, but headache, dizziness and minor disorder of the functions of intellect and emotion may sometimes occur without loss of consciousness, and the absence of such symptoms in the first 24 hours does not exclude the possibility of their later appearance.

Prognosis after the Acute Stage

The division of prognosis into two stages is artificial but convenient, for after the patient has regained clear consciousness, but not until then, it is possible to assess the duration of the post-traumatic amnesia, which is the most clearly defined and useful guide to prognosis at present available. The retrograde amnesia (the loss of memory for events immediately preceding the accident) is usually no longer than a few minutes, it may in cases of severe injury be much longer, extending up to days or weeks, but tends subsequently to shrink. It has been considered (Symonds, 1943) that a final retrograde amnesia of long duration is commonly associated with incomplete restoration of mental function, but as the final estimate can be made only after several weeks or months it is of little prognostic value. The post-traumatic amnesia on the other hand, which should be measured from the moment when the patient became *continuously* aware of and able to remember his surroundings, shows no alteration with the lapse of time and can be finally assessed when the patient is well enough to co-operate in the enquiry.

Russell (1932), who first used this method of grading the severity of closed injuries, followed up a consecutive series of patients admitted to hospital and observed in the acute stage, for an average period of 18 months (Russell, 1934). In all these cases there had been initial disturbance of consciousness. Symptoms attributable to the injury were still present in 60% at the end of 2 months, and after 18 months in 40%. Of 112 working men and women of the series with no compensation claim arising from the injury, 83% had returned to full work within 6 months of its occurrence and only 9% remained unfit for full work after 18 months. In the compensation cases, the duration of disability was considerably longer. These figures show what is probably true for any group of closed injuries severe enough to be admitted to hospital (excluding those which end fatally), that though symptoms frequently persist for a year or more they are rarely disabling for longer than 6 months. The prognosis with regard to the duration of disability was worse in patients over the age of 40. Excluding these, in the non-compensation group, 95% of the cases with a post-traumatic amnesia (PTA) of less than 1 hour returned to work within 2 months, with a PTA of more than 24 hours, the chances were against the patient being fit for work within 2 months, but 80% of such patients were able to resume full work within 6 months.

Guttman (1943b), in a consecutive series of cases admitted to a civilian hospital in a provincial area during the war, found that in 130 wage-earners the loss of working time was as follows: 25% of patients lost 3 weeks or less, 50% between 3 and 9 weeks, 25% more than 9 weeks. Basing prognosis upon the duration of the PTA, Guttman found that with a PTA of 1 hour or less the expectation of disability was about 4 weeks, with a PTA up to 24 hours, about 6 weeks, and with a PTA up to 7 days 8 or 9 weeks. The data, however, are not comparable with Russell's for Guttman excluded cases complicated by injuries to other parts of the body, while these were included in Russell's series.

Symonds & Russell (1943), relating the ultimate disposal of 955 service patients with closed injuries, admitted to a hospital for head injuries, to the duration of the PTA, divided them into two groups: those who were admitted within 3 weeks of the injury (acute cases), and those who were admitted later on account of the severity of their symptoms, complications, or unsatisfactory progress (chronic cases). Among the acute cases with a PTA up to 24 hours 12% were invalided, for a PTA between 1 and 7 days the invaliding rate was 24%, and for a PTA over 7 days, 60%. In the 'chronic' group the percentage of cases invalided having a relatively short PTA was much higher, the figures ranging from 49% for a PTA less than 1 hour to 60% for a PTA over 7 days.

Symonds (1937a, 1937b) had previously emphasized the importance of individual constitution as a prognostic factor, observing that neurotic predisposition carried a greater risk of prolonged invalidism. Such predisposition was assessed in both groups of the series reported by Symonds & Russell (1943), and its incidence was found to be twice as high in the chronic as in the acute group. It was concluded that this factor was probably responsible for the worse prognosis in the chronic group (52 % invalided as opposed to 20 % in the acute group) of patients whose injury measured by the average duration of PTA had been no more severe than in the others, but who were transferred from other hospitals because their progress was unsatisfactory. In a group of 111 R A F aircrew (acute and chronic cases) 18 % showed evidence of neurotic predisposition, in a comparable group of other soldiers and airmen the figure was 38 %. The corresponding figures for invaliding were 12 % and 48 %, including those invalided in hospital and those who relapsed after discharge and were invalided later. These observations confirm the impression that the neurotic individual is more vulnerable to head injury than others.

Cairns (1942) has proposed that the length of PTA should be used as a rough measure of the shortest time in which ability to carry out full work may be expected to return as follows

PTA	Months after which full work may be resumed
5 minutes-1 hour	1-1½
1-24 hours	1½-2
1-7 days	2-4
over 7 days	4-8

Symonds (1942) believes that the length of PTA as a measure of prognosis, although of undoubted value, may be fallacious and should be used with caution, arguing that on the one hand many patients with a PTA of 1 hour or less are completely recovered within a few days, and that on the other hand a man with a brief PTA may suffer prolonged disability as the effect of local cerebral contusion. He considers that it is unjustifiable to assume that neurotic symptoms in a man with a brief PTA are wholly due to psychological causes.

Lewis (1942) supports this view, arguing that the symptom-pattern of psychological disorder furnishes no reliable clue to its cause, which may be brain injury, or psychological reaction, or both. The individual who has neurotic predisposition is more apt to suffer prolonged disability than others, because (a) the effects of injury upon his brain are more likely to impair his capacity for psychological adjustment, and (b) he is less well equipped *ab initio* for making adjustments to the psychological trauma of his accident, its effects upon his life situation, and whatever physical disability may have resulted. Other writers (Denny-Brown, 1942, Guttman, 1943a) are inclined to the belief that psychological disorder after closed head injury, when the PTA has been brief or there is no other evidence of organic cerebral damage, may be assumed to be psychogenic. There is at any rate widespread agreement (O'Connell, 1941, Symonds, 1941, Denny-Brown, 1943a, 1943b, Schilder, 1934) that a critical examination of the family history and pre-traumatic personality for evidence of a liability to psychological disorder is an indispensable guide to prognosis.

Examination of the intellectual functions after the acute stage may reveal impairment, as judged either by subsequent improvement or by an estimate of the pre-traumatic intellectual capacity. Ruesch (1944) has observed that the frequency of intellectual impairment observed after the acute stage is closely related to the duration of coma, semi-coma, and confusion. Of the tests used, he found the 100-7 test, pictorial absurdities, hole-in-the-board test, pictorial discrimination, naming of colours, and reading the most reliable. The mental functions chiefly affected were speed, judgment, and ability to maintain effort. About one-half of a series of patients studied by these methods showed intellectual impairment, which became less marked with increasing remoteness from the time of the injury. If the impairment was reversible, its duration was usually less than 3 months. Reynell (1944), using a differential test, based upon the observation of Wechsler and others that vocabulary, general information and comprehension were less affected by organic cerebral disease than arithmetical reasoning, memory and relational thinking, has concluded that a measure of intellectual impairment can be arrived at by this method, which is a reliable guide to the prognosis for return to military duties.

Although there seems to be general agreement that permanent total incapacity from intellectual impairment after closed head injury is very rare, we have at present no indication of the frequency of a permanent reduction in the intellectual level or the early symptoms from which this might be foretold. There is a comparable lack of data for the prognosis of personality-disorder of non-incapacitating degree, though the impression of experienced clinicians (Schilder, 1934, Mapother, 1937, Bowman & Blau, 1943) is that this is not an infrequent residuum. It is to be hoped that investigations now in progress may fill these serious gaps in our knowledge.

Russell (1934) found that the duration of disability increased with age, in his series of 200 cases, 6 % of the patients between the ages of 15 and 30 were unable to do full work 18 months after the injury. The corresponding figure for those between 30 and 50 was 21 % and 46 % for those over 50.

The nature of the occupation to which the patient must return has obvious bearing upon the duration and amount of disability. Problems in this connection have been fully discussed by Goldstein (1942).

Concerning the prognosis after the first 24 hours in the patient with a closed head injury who has not been unconscious, there is little to be said except that the index of the PTA is lacking. Signs of focal cerebral lesions or cranial nerve palsy are extremely rare in these cases, for the injury would have to be of an exceptional nature to cause such focal lesions without concussion, although local indentation of the skull, as by a hard ball, or slow lateral compression, may do this. Headache, dizziness and psychological disorder may occur without disturbance of consciousness, and sometimes after a latent interval. The prognosis will then depend upon the other points which have been mentioned. The assessment of the pre-traumatic personality furnishes the best guide.

Williams (1941b) has studied, with the electroencephalogram (EEG), a large series of cases after the acute stage and has found abnormalities in 50 %. Improvement in the EEG is usually closely related to clinical recovery, but in some cases the EEG may remain abnormal after clinical recovery appears complete, and this is taken to indicate the continued presence of damaged brain tissue, and the need for anticipating symptoms of relapse when the patient returns to duty. A normal EEG after head injury indicates the absence of damaged brain tissue, which may be due either to full resolution or to complete destruction of damaged cerebral substance. When a normal EEG is associated with full clinical recovery, prognosis is consequently good, but when it is accompanied by persistent symptoms the prognosis may be bad.

Prognosis with Regard to Individual Symptoms

Although it had been supposed that *headache* was an almost universal symptom, Russell (1932) observed that complete absence of headache in cases of both slight and severe injuries was not uncommon. In 173 cases of his series in which data were available, it was recorded as absent in 64, moderate in 48 and severe in 61. Guttman (1943a) in a series of 158 civilian cases admitted to hospital and followed up after their discharge found that less than half the patients had headache on recovering consciousness and that the complaint was less frequent in those with a long PTA. On discharge from hospital, the incidence of headache was 21 %, "when expected to be fit for work" 38 %. Three months after the accident, in patients who had resumed work, the incidence of headache was 21 %, and 6 months after the accident it was 18 %.

Anosmia was recorded in 72 of a series of 1,000 cases of head injury studied by Leigh (1943). In 41 of these the anosmia was bilateral and complete, and in the remainder unilateral or partial. In only 6 cases was any recovery of smell noted. Three of these patients experienced parosmia as a preliminary to recovery. In 9 other cases of the series, parosmia was noted without subsequent recovery of smell. Of the 6 cases which proved to have a good prognosis 5 had recovered within 4 months of the injury, the other taking 12 months to recover.

Turner (1943) from a study of 46 cases of indirect injuries of one *optic nerve* in head injuries concludes that even when the nerve is only partially damaged there is often complete loss of vision in the affected eye for two or three days before recovery begins. If there is to be a useful degree of recovery

of vision, improvement usually starts about the 3rd or 4th day and rapidly progresses. By the 4th week after the injury, all the recovery that is going to occur will usually have taken place. In one half of his cases, final visual acuity was less than 6/60, in rather less than one-third it was 6/12 or better.

Lyle (1941) considers that if *diplopia* following head injury has not recovered spontaneously within 4 months, it is unlikely to do so, and surgical treatment is indicated to correct the ocular deviation by appropriate operation upon one or more of the extrinsic ocular muscles.

Turner (1944) has studied the prognosis of *facial palsy* in a series of 70 consecutive cases of closed head injury with this complication. In 34 of these cases the onset of the facial palsy was delayed, being observed between the 2nd and 8th days after the injury. In these cases with delayed onset, good recovery occurred in all except 2. In three-quarters of these cases with a good prognosis, improvement was evident within 3 weeks of the injury. Of the 36 cases in which the onset of the facial palsy was immediate, one quarter showed incomplete or no recovery. Of the 27 cases which made a good recovery, 24 showed improvement within 3 weeks of the injury and complete recovery within 8 weeks of the injury. In the 3 remaining cases improvement began within 6 to 8 weeks with complete recovery within 3 months of the injury.

Prognosis with Regard to Epilepsy

The occurrence of epilepsy after closed head injury has been generally recognized. Its frequency, however, is in doubt, as also the possibility of forecasting the probability of its occurrence in the individual case. These questions are of practical importance, for the first fit may occur months, or it may be years, after the injury. Thus, the patient may appear to have recovered from the original effects of the injury but develop a severe disability later. In the settlement by a single payment of a claim for compensation arising from the accident, this risk should be covered, but its computation at present is a matter of great difficulty. The main reason for this is lack of uniformity in the case-material upon which the available figures have been based.

The incidence of epilepsy after gunshot wounds with and without penetration of the dura has been carefully studied, but has no bearing upon the present discussion, for high-velocity missiles without penetration of the dura appear to be followed by epilepsy much more often than the blunt injuries of civilian practice. In Russell's series (1934) of 200 cases of closed injury followed up for 18 months, the incidence of epilepsy was 3.5%. Rowbotham (1942) followed up 430 patients who had been admitted to hospital for closed head injuries of the blunt type at least 5 years previously, and found that 2.5% had developed epilepsy. Feinberg (1934) found 50 cases of traumatic epilepsy in 47,130 cases of head injury reported to a Swiss insurance company during a period of 14 years—approximately 1 per 1,000. This series is not comparable with those of Russell and Rowbotham, as it includes a very large number of trivial injuries. In 3,906 cases with fracture of the skull Feinberg found the incidence of traumatic epilepsy 5 per 1,000 and in 16,762 cases of concussion without fracture 1.25 per 1,000. He excluded all cases of epilepsy following the injury in which there was a positive family history, other possible causes (e.g. alcoholism), or what appeared to be an inadequate injury. All who have written on this subject are agreed that the interval between the injury and the first fit is commonly more than 1 year and may in some cases be many years.

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The relation of the risk of later development of traumatic epilepsy to the symptoms immediately following the injury has been discussed by several writers (Symonds, 1935; Garland, 1942; Denny-Brown, 1944). Symonds concluded that skull fracture, a long PTA, fits in the first week or two after the injury, signs of focal cerebral damage, persistent intellectual impairment and personality disorder, and a continued liability to headache, were all of more frequent occurrence in patients who developed late epilepsy than others. In this connection, the prognostic import of fits occurring in the early stages was first discussed by Wagstaffe (1928). Contrary to the general opinion held at that time that early fits were of no importance in the prognosis of traumatic epilepsy, he observed in a follow-up of 340 cases of gunshot wound that late traumatic epilepsy was much more common in the cases showing transient fits in the few days after the injury. Comparable data for closed injuries of the blunt type, in which early fits are of much less frequent occurrence than in gunshot wounds, are at present lacking.

Denny-Brown (1944) in a study of 630 cases of head injury, mostly of the closed type, observed that of 87 patients whose PTA lasted more than 7 days, 3 (3.4%) became epileptic, of 151 patients with 1–7 days of PTA, 7 (4.6%) became epileptic, and of 392 patients with less than one day of PTA, 45 (10.9%) later had fits. The incidence of epilepsy in the whole group was 8.3%, but the series included cases admitted to a special military hospital for head injuries because of unusual or late complications, so that the total figure of incidence is not a fair sample. Denny-Brown argues that, as the length of the PTA is an index of the general disturbance of the brain caused by the injury, the figures which have been quoted indicate that local and not generalised brain damage is the most important factor in epilepsy, and offers in support of this view the observation that there has usually been some evidence of local contusion or laceration.

General Conclusions

In estimating the prognosis in closed head injuries, the physician or surgeon must take into account first, the extent and severity of the cerebral injury as measured by the depth and duration of the disturbance of consciousness, and any evidence of focal damage, and second, by an assessment of the patient's symptoms when he is able to express them, the measurement of intellectual impairment and the estimate of personality disorder. Of no less importance is the psychological stability and stamina of the individual before the injury, as shown by his family and personal histories. Methodical examination of the nervous system is necessary to discover signs of local brain injury or damage to cranial nerves of prognostic importance. x-rays, examination of cerebrospinal fluid and EEG, especially the last-named, may sometimes provide valuable information.

In many cases it will be necessary to get the patient back to his normal mode of living and occupation and watch his progress before the final prognosis can be determined. One cannot discover whether the brain has recovered its normal functions until one has observed it at its normal work. Even when the patient appears to have made a complete recovery there is a possibility that traumatic epilepsy may develop later. Prognostic criteria for this important complication are at present inadequate, and the task of elucidating this and many other problems of prognosis can be fulfilled only by the close and unremittent co-operation of surgeon, neurologist and psychiatrist in large series of cases followed over long periods.

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THE CLINICAL APPLICATION OF ELECTROENCEPHALOGRAPHY

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Shortly after the publication of Hans Berger's (1929-37) classical researches into the electrical-potential changes which he had recorded from the human scalp, and after his results were confirmed in other countries, his discoveries were applied to the problems of clinical neurology and psychiatry. This work was stimulated by the fact that Berger (1933) had described distinct differences in the cerebral electrical patterns of certain abnormal subjects, and of normals. Physiological investigations into the phenomena which Berger had described were undertaken in Cambridge, where Adrian and his colleagues studied in great detail the origin and methods of spread of the waves. Adrian & Matthews (1934b) described the characteristics of the normal waves in man, Adrian & Yamagiwa (1935) studied their point of origin, and Adrian (1936) later described their method of spread from their focus of discharge in the parieto-occipital region.

The ease with which the electroencephalogram (EEG) could be recorded in man simplified the study of its characteristics in various abnormal states, but this technical advantage led in some instances to carefree and rather uncritical application to clinical problems. The first important advance upon Berger's observations took place in 1935 when Gibbs, Davis & Lennox described the electrical discharges associated with an epileptic attack. At almost the same time Hoagland and workers in other centres were describing abnormal features in the EEG of psychotic patients (Hoagland, Cameron & Rubin, 1937). Another important advance took place in 1936 when Walter described a method of localizing intracranial lesions by means of the abnormally slow waves which he was able to record from damaged brain in the neighbourhood of a cerebral tumour. After this time interest in the clinical uses of the EEG rapidly increased, particularly in the United States of America.

During the present war there has been an enormous extension of the clinical use of the electroencephalogram, and the number of centres in the British Isles employing it, which now approaches twenty, is at present limited by the difficulty in obtaining the necessary apparatus. Nearly all the centres are asked to investigate more cases than they can handle. The laboratories which exist are nearly all established in large neurological or psychiatric hospitals, and the work is carried out in very close association with the clinical workers. The Electroencephalographic Society was formed two years ago under the presidency of Professor Adrian. Besides providing facilities for discussion and for presentation of original papers, the Society has aimed at the standardization of interpretation and of the nomenclature of the subject. There is now general agreement upon the broad principles of clinical electroencephalography, although much of the interpretation is necessarily still empirical. Because of limitations upon academic research imposed by the war, much of the original work published in Britain in the last few years has a clinical flavour, and experimental work in this field is uncommon.

Reviews of the subject have been written by Jasper (1937), Walter (1938), Bremer (1938), Balado, Romero & Noisieux (1939), Baudouin & Fischgold (1939), Gibbs & Gibbs (1941) and Lindsley (1944). These should be used for a fuller understanding of the subject, for it is possible to give only the most general impressions of the clinical use of the EEG in this short review.

Technique

The method usually employed in Britain is to record from the intact scalp, the patient sitting or lying down, with saline-pad electrodes securely held in place by a cap of elastic or of rubber and whalebone bands. To make a good electrical contact, the scalp is cleaned with ether and then saline. Usually 16 saline-pad electrodes are placed in position over the convexity of the hemispheres in 4 rows from before backwards. Records are made by comparing, through a condenser-coupled amplifier, the potential difference between each adjacent pair of electrodes. This is known as bipolar recording, in contrast to monopolar, where the potentials at one point of the scalp are compared with those at a relatively inactive area, such as the ear. Sometimes silver or solder electrodes are sealed to the scalp, the advantage over saline pads being the security of the contact, and the disadvantage the time involved in preparing the subject for recording. This method is widely used in the United States, where monopolar recording is also customary. Records are made, as a rule, by ink-writing oscillographs, 3 or 6 simultaneous tracings being obtained. It is rarely necessary to use cathode-ray oscillographs or a light source for recording for clinical purposes. The technical methods have recently been described in some detail by Parr & Walter (1943). Elaborations in recording have been described by Beevers & Furth (1943a, 1943b) who devised an apparatus called the encephalophone, which converts the electrical-potential changes into sound waves, and by Walter (1944a) who has designed an admirable piece of apparatus which provides an electrical analysis of the records. This apparatus is simpler than an earlier one designed for the same purpose by Grass & Gibbs (1938). Such a wave-band analysis should greatly simplify some aspects of the clinical interpretation of the EEG, and some of the results of its use have already been described (Walter, 1944a, Dawson & Walter, 1944). Most of the original papers dealing with the technical and physical aspects of electroencephalography which are written in Britain are now published in the journal *Electronic Engineering*.

Interpretation

The use of the EEG in clinical medicine depends at present entirely on direct visual interpretation of the records, which show a very complex pattern of superimposed wave forms. This interpretation will of course be greatly helped by using Walter's method of wave-band analysis. Even so, study of the total record gives much information which cannot be obtained by analysis alone. There are, however, some features of abnormal records, such as the discharges which accompany epileptic activity—"larval epileptic attacks"—which are so distinctive that when they are present they make the correct interpretation of the EEG virtually certain. In other cases the clinical interpretation of the EEG must depend upon a careful appraisal of all its features, considered as a whole, and assessed against the background of the other clinical findings. In addition there is no certainty that any group of phenomena in the EEG, with the exception of larval epileptic outbursts, has any specific meaning. In consequence all sources of information, the EEG, the clinical signs, chemical studies, x-rays, and the patient's story, must be integrated to reach a reasonable conclusion, in exactly the same way as in other fields of clinical investigation. A

further difficulty exists in the fact that a considerable fraction of the normal population has abnormal EEG records, while varying fractions of patients with different kinds of illnesses have normal records. It follows from this that any attempt to use the EEG by itself to give a diagnosis will be unsatisfactory, and will bring a most valuable clinical tool into disrepute. Full clinical notes should be available at the time of interpretation of the records, and the clinician should consider the EEG findings in relation to the complete clinical picture, in the same way as a physician relates the x-ray appearances of a chest to the clinical signs.

Normals

A significant proportion of apparently normal subjects have abnormal features in the EEG, examples of two kinds of abnormal records are shown (Fig 1a, 1b). By the standard which is most widely accepted, this proportion is about 12% but the number of subjects with abnormal records depends upon the manner in which the population has been selected (Williams, 1941c). For instance, subjects who are apparently normal may be the near relatives of epileptics or psychotics, and there is no evidence that others who are judged to be normal may not develop a psychological illness or epilepsy later in life. There are many studies (e.g., Lindsley & Cutts, 1940) which suggest that these subjects, although apparently normal, include a higher proportion with abnormal EEGs than others.

Abnormals

Criteria of abnormality have been published in the report of the council of the Electroencephalographic Society for 1944. It is probable that these criteria may have to be modified as experience widens, and as wave-band analysis becomes more extensively used. Full descriptions and examples of the features of normal and abnormal EEGs have also been given in the *Atlas of electroencephalography* (Gibbs & Gibbs, 1941). Abnormal waves may be slow, fast, or a mixture of both, sometimes they even have the same frequencies as normal waves, but their position, voltage or shape may be abnormal. They may be persistent or episodic, as in some epileptics. They may be focal, as they often are in the neighbourhood of a tumour, an abscess, or a penetrating head injury, or they may be generalized as they are in high intracranial pressure, intoxications, deep sleep or coma (see Fig 2a).

The degree of abnormality which is recognized in these waves depends in part on their form, the manner in which they are linked together, their amplitude, their frequency and their persistence. Their position over the scalp may also be important, as well as the way in which they respond to physiological changes such as opening the eyes or over-breathing. It has been mentioned that some abnormal features in the EEG are specifically related to an abnormal state such as epilepsy (Fig 3a, 3b, 4a), but most have no specific pathological importance, they simply indicate the presence, position and extent of deranged cerebral cortex (Fig 2a, 2b, 4b). Williams (1944a) makes a distinction between abnormalities in the EEG which arise as a direct result of cerebral damage—for instance a head injury—and those which arise indirectly, and which may be associated with epilepsy or other behaviour disorders. They have different physical and physiological characteristics, and an entirely different clinical significance.

Intracranial Lesions

Walter showed in 1936 and 1937 that the abnormal cortex in the neighbourhood of cerebral tumours could be localized by the EEG. He developed a technique, originally devised by Adrian and Matthews for studying the faster normal waves, which made use of the phase-reversal of waves recorded from electrodes placed on each side of the point of propagation. Other workers amply confirmed his results (Williams & Gibbs, 1939, Cobb, 1944), and his method is now widely used. In this method, use is made of the presence of abnormally slow waves (between $\frac{1}{2}$ to 7 per second) in the neighbourhood of the lesion (Figs 2b, 4b). The frequency and amplitude of the waves and their phase-reversal are utilized to localize the lesion (Fig 4b). There has been no advance in the technique of localizing cerebral lesions since that time, although interpretation of the results has progressed. Suppression of the normal frequencies over an area of damaged brain can also be used in the same way (Jasper, Kershman & Elvidge, 1940) while, less frequently, abnormally fast waves may indicate the position of the lesion.

The EEG findings may be correlated with the history and the clinical signs to aid in the differential diagnosis of the nature of the lesion. The EEG alone cannot be of any value for this purpose, for the changes produced depend upon the severity and extent of the cerebral dysfunction, and not upon the nature of the causal lesion. Acute lesions, such as abscesses, consequently produce more dramatic changes. The local abnormality may be masked by a generalized disturbance which may be the result, for instance, of high intracranial pressure. In this condition the abnormal slow waves are not caused by the pressure alone, but are the results of a secondary change in the cerebral hemispheres, which can be reversed by dehydration (Williams, 1939).

Negative results may sometimes be obtained when an intracranial lesion is present if the lesion is very small, deep, inaccessible to exploring electrodes—as it would be on the under-surface of the temporal lobes—or when it is not causing any destruction of cerebral tissue. Sometimes a meningioma of the convexity of the hemispheres may give minimal changes in the EEG which may easily be overlooked in interpreting the records. In these circumstances the EEG should not be considered to have failed in its purpose, for if the negative result is related to the clinical picture and x-ray findings it should help in the recognition of the benign nature of the tumour.

Similarly, if the EEG shows severe dysrhythmia in the frontal lobes, and the observer fails to lateralize the point of origin of the abnormal waves, in a case in which a frontal tumour has been demonstrated on one side by other methods, the result should not be considered as failure to localize the tumour. It is almost certain evidence that the tumour has involved the corpus callosum and has become bilateral. Used in this way, the EEG may provide useful evidence about the nature of the lesion before operation is undertaken. At operation, findings which were previously obtained through the intact skull may be confirmed by direct exploration of the cortex with a wick electrode (Jasper, 1941).

The indirect changes in the EEG which may result from intracranial lesions, and which are so often associated with epilepsy, are mentioned later. Walter & Dovey (1944) have recently described waves which they have called "theta" waves, which are recorded from the surface of the hemispheres when deep lesions are present.

Cerebral Trauma

In general, the changes which result from cerebral trauma have the same characteristics as those produced by other forms of cerebral insult. The form of the slow waves, and the suppression of the dominant frequency, are indistinguishable from those seen around tumours or abscesses (Jasper, Kershman & Elvidge, 1940), but when the EEG findings are related to the other clinical signs, some changes characteristic of head injury may be recognized. Serial records made during recovery show that there is a transition in the EEG from very slow waves of relatively high voltage, dominating the whole record, through stages in which the slow waves increase in frequency, decrease in size, and become less and less persistent, until the normal frequencies make their appearance, and the record is finally judged to be normal (see Fig 2a, 2b). These changes have been fully described by Williams (1941a, 1941b).

In a closed head injury in which concussion has occurred, abnormally slow waves can be recorded from all points on the hemispheres, although they may later become more evident at the site of injury. Contrecoup effects can be easily recognized in the EEG, and most unexpected areas of damage may be unmasked (Fig. 2b). Foci of abnormal waves have also been recorded around wounds of the scalp which were thought to be trivial, but which had, nevertheless, been associated with slight and unsuspected brain damage (Bickford, 1945). In penetrating head injuries, the abnormalities may be confined to the area around the wound, but here again when concussion has occurred in association with the penetrating brain wound, these focal waves may be associated with a generalized disturbance. There is no difference between the general characteristics of an EEG recorded from the neighbourhood of a penetrating or focal brain injury and those, recorded from any point on the scalp in a patient who has had a generalized closed head injury.

In about half the patients who have a persistence of symptoms after injury, abnormalities also persist in the EEG.

In all the figures, the horizontal line represents 1 second, the vertical signal 50 microvolts

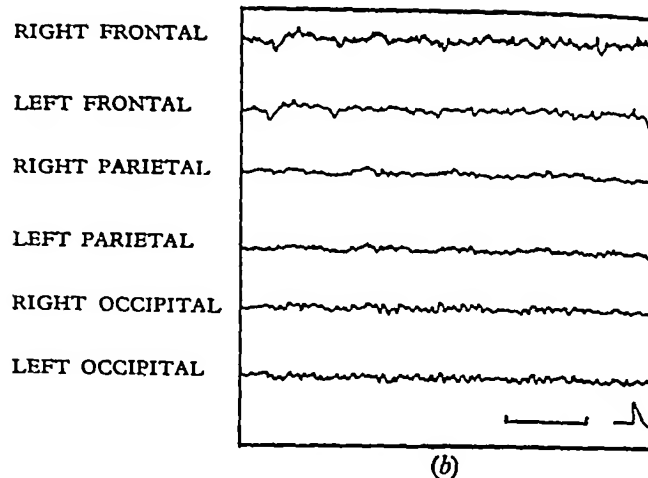
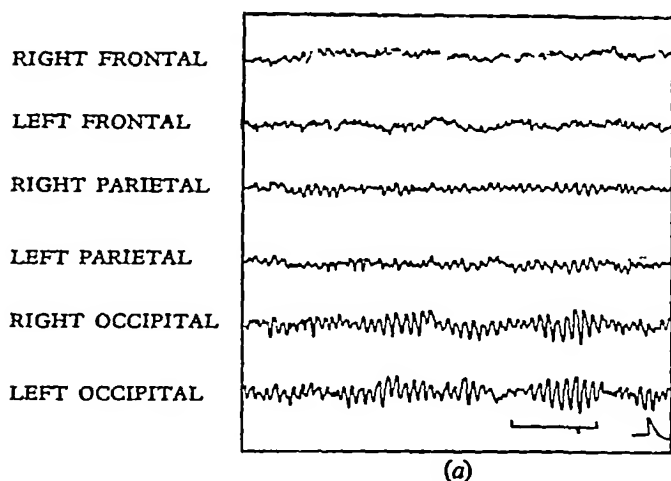


FIG 1 Normal records (a and b), recorded on six ink-writing oscillographs. 1a shows a frequency of 10 per second of relatively high voltage arising in the occipital lobes. This frequency is only just apparent in the other set of normal records.

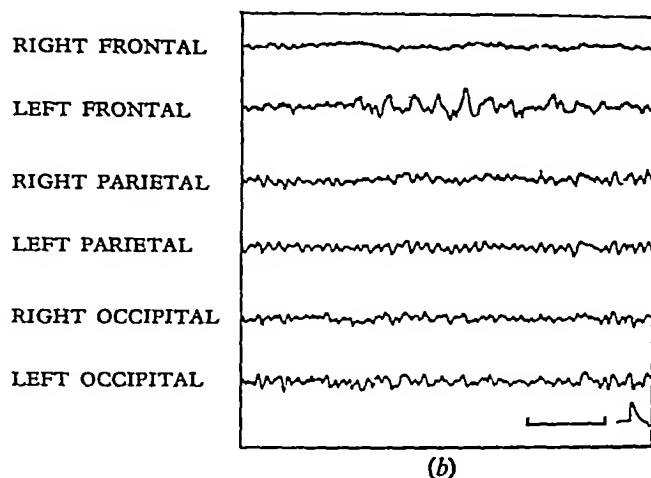
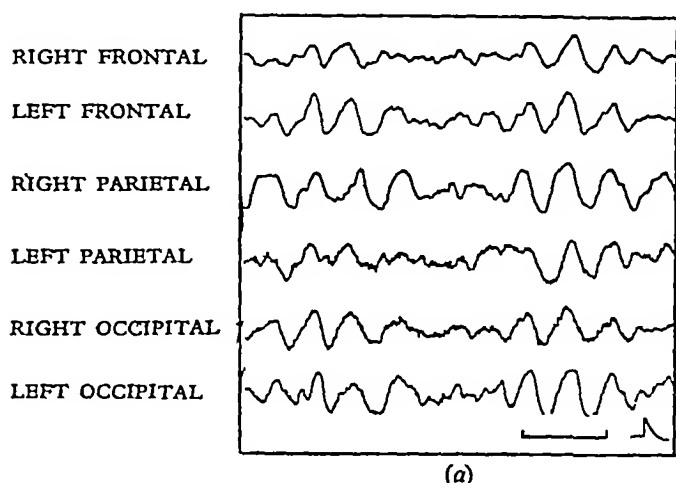


FIG 2 Records obtained 3 days (a) and 3 weeks (b) after a closed head injury of moderate severity. In (a) there are runs of very high-voltage 2-cycle sine waves spreading all over the hemispheres. Within 3 weeks (b) these waves have completely disappeared and are replaced by runs of low-voltage 4-per-second waves in both occipital poles, and a focus of abnormal slow waves in the left frontal lobe. The normal dominant frequency of 9 per second has returned. What has happened in the interval between the two records is that the very slow waves have gradually been replaced by faster ones of progressively lower voltage, and simultaneously the normal rhythms have returned. Abnormal waves resulting from an unsuspected focal contusion have been unmasked in the left frontal pole.

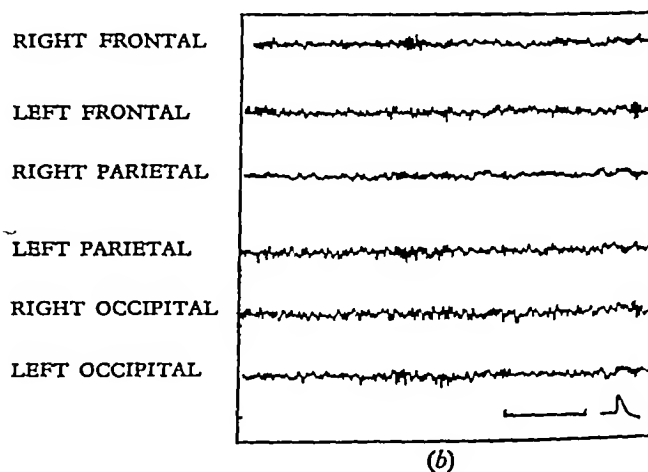
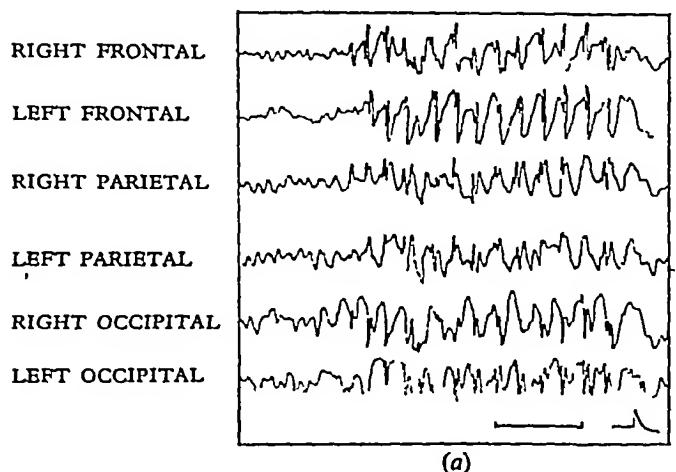


FIG 3—Records from two patients with idiopathic epilepsy. At (a) there is an outburst, occurring simultaneously in all leads and lasting for 4 seconds, of high-voltage waves of 3 per second, alternating with spikes. At (b) there is an outburst in all leads, lasting for 5 seconds, of 25-per-second waves. Both these disturbances represent epileptic outbursts.

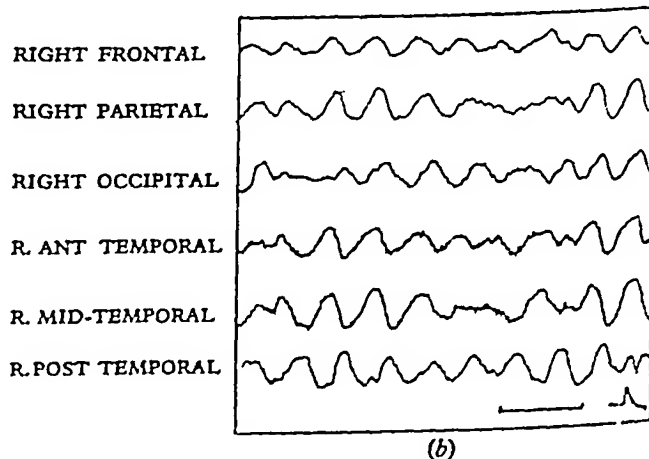
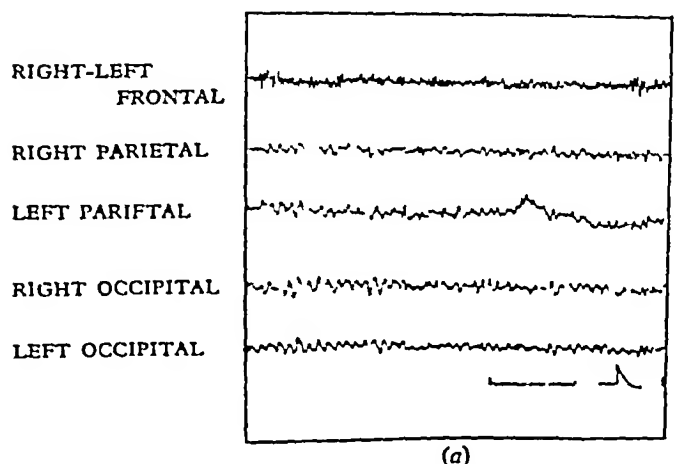


FIG 4 (a) Records obtained 5 weeks after a penetrating parietal head injury show episodes of abnormal 22-cycle waves, confined to records from the frontal poles. The patient had had one epileptic attack, and the fast waves represented epileptic activity. This kind of disturbance is often recorded before the onset of traumatic epilepsy. (b) Abnormal 22-cycle waves recorded shortly after a severe closed head injury. The electrodes have been placed in two rows anterior-posteriorly on the right side as the patient was lying on his side, unconscious. A phase-reversal is clearly seen between the records obtained from the right mid- and posterior temporal regions. Such a phase reversal of the waves indicates their pole of origin and is used in localizing cerebral lesions.

(Williams, 1941b) Heppenstall & Hill (1943) have shown that, when these persisting abnormal waves have a focus of origin, they have usually been caused by the injury, but that when the waves are generalized and have no focus they may have been present before the injury. In these circumstances they may be an indication of a constitutional defect in the subject (*vide infra*). Areas of suppression of the normal waves are seen around local injuries, and in some instances where the trauma has been slight, this may be the only abnormality present. These silent areas may also occur over subdural haematomas (Jasper, Kershman & Elvidge, 1940), but they are also found over other large intracranial lesions.

Epilepsy

The extensive studies by Gibbs and Lennox of the cerebral electrical changes associated with epilepsy have been summarized in Gibbs' *Atlas of electroencephalography*, already quoted. Opinions upon the meaning of some of the phenomena which have been observed have undergone several changes in the last few years, and the review written by Jasper in Penfield & Erickson (1941) *Epilepsy and cerebral localization* shows that many questions are still unsettled, while Finlay & Dynes (1942) have disagreed with some of Gibbs' earlier interpretations of the EEG recorded in epileptics.

Most workers now agree that some epileptic patients show normal EEGs although it is likely that if the records are repeated often enough the EEG of every epileptic would show characteristic changes. It must be remembered that whether or not an observer considers a record abnormal depends upon the standard which he has adopted, this observation applies particularly to borderline records. Using a norm which is generally accepted in this country Williams (1944b) has found that 75% of idiopathic epileptics show abnormalities at any one time, compared with 12% of unselected normals. The abnormalities seen in the EEG of epileptics may be either episodic or continuous (Fig 3a, 3b). The episodic disorders are the electrical counterparts of attacks which may sometimes be of so short duration that they cannot be detected by ordinary clinical methods, but Schwab (1939) has shown by more elaborate methods of testing that interruption in the stream of consciousness occurs with the most evanescent disturbances in the EEG. Dawson (1944) has also shown in patients with myoclonic epilepsy that single rapid spikes which may be recorded in the EEG are accompanied by single motor unit discharges in the affected muscle which may be taken to represent minute epileptic attacks.

The clinical type or types of epilepsy from which a patient is suffering cannot be predicted from the form of the discharges in the EEG. When the EEG is recorded during a clinical attack, it is seen that there is a close relationship between the actual pattern of the observed epileptic attack and the form of the electrical disturbances which accompany it. The explanation of this anomaly is that, although some patients only experience one kind of attack, other kinds of which they are not aware may be represented in the EEG.

There is not space here to describe the classifications which have been devised for the abnormal discharge seen in the EEG of epileptics. Gibbs has based his division on the wave-forms seen in the discharges, and on the clinical form of the attacks which are most usually associated with those forms, whereas Jasper has devised a classification based entirely on the EEG findings. This division depends on the wave-form and the position of origin of the discharge. There are also many differences in the behaviour of the different types of epileptic discharges in response to physiological changes.

There is a constant difference between the EEGs of idiopathic and symptomatic epileptics, although some kinds of disturbance, for example the "wave and spike" complex (Fig 3a) seem to be confined to patients who have had an epileptic tendency of very long standing. These disturbances are most usually met in childhood, or in adults who have had fits since childhood, and their response to physiological changes is very different from that of other forms of epileptic disturbances seen in the EEG. Study of this form of discharge fails to show any difference between pyknolepsy and petit mal.

Foci of abnormal discharges have repeatedly been described in epileptics (Jasper & Kershman, 1941, Gibbs, Merritt &

Gibbs, 1943) and focal abnormality is more frequently seen in symptomatic than in idiopathic epilepsy (see Fig 4a).

There is such an extensive literature upon the EEG changes in relation to epilepsy that it cannot be covered here. Particularly interesting advances have been made in relation to heredity (Lennox, Gibbs & Gibbs, 1939, Lennox, 1940, Strauss, Rahm & Barrera, 1939) and pharmacology (Gibbs, Gibbs & Lennox, 1939).

Traumatic and symptomatic epilepsy requires individual consideration, for in traumatic epilepsy the gradual development of the epileptic state can be observed by recording serial EEGs over a period of months or years after the injury (Williams, 1944a). The abnormally slow waves which are the direct result of cerebral trauma slowly resolve as recovery from the injury takes place (Fig 2a, 2b). Later on episodes of abnormal waves of a different kind make their appearance, and these gradually become more evident and more frequent. Finally, a clinical fit may be observed. These episodic disturbances, which are an indirect result of the injury, and which do not occur in all cases of head injury, require weeks or months for their development. Sometimes they arise in the zone of maximal brain damage, but more commonly they are symmetrically placed in the frontal or parietal lobes without any evident spatial relation to the injury (Fig 4a). Adequate removal of damaged brain seems to prevent the recurrence of these disturbances but the effect of prophylactic anticonvulsant drugs is unknown. A normal EEG is more commonly seen in traumatic epileptics than in idiopathic epileptics, and consequently a normal EEG after a head injury does not exclude the possibility of traumatic epilepsy. Focal discharges are also more common in traumatic epileptics (Fig 3a, 3b, 4a).

Behaviour Disorders

The researches in this field may be divided into those concerned with (i) apparently inborn behaviour-disorders in children, (ii) neurosis, (iii) psychopathy, (iv) organic psychosis, (v) criminal behaviour.

At present the clinical application of all this work is necessarily tentative, and is mainly concerned with diagnosis and aetiology. It is handicapped by the morphological similarity of the EEG in all these conditions, and by the fact that in each group a high percentage of patients have normal records. As there is no apparent difference between the patients in any of the first four of these groups with normal or abnormal records, the difficulties are considerably increased. In most of the disorders, for instance psychopathy, the clinical diagnosis is readily apparent, but the underlying aetiological factors are not understood. The EEG has so far proved of value in demonstrating an aberration in cerebral function which exists in association with the behaviour-disorders. In many cases these disorders might otherwise have been considered to be entirely the result of psychological trauma.

It has also shown that relationships do exist between apparently different and unrelated kinds of behaviour-disorder. An instance of this is seen in the relationship which has been demonstrated between aggressive psychopathy, which has been studied by Hill & Watterson (1942), and epilepsy. About half the subjects showing aggressive antisocial behaviour have an abnormal EEG (Hill & Watterson, 1942), and some of the episodic disturbances are indistinguishable from those associated with epilepsy (Hill, 1944). This overlap between psychopathy and epilepsy, which was recognized by workers concerned primarily with psychopathic behaviour, was also appreciated by others who were mainly interested in epilepsy (Williams, 1944c).

Although specific inter-relationships of this sort can be recognized, a serious difficulty that exists in interpretation of the EEG is that most of the abnormalities seen in the EEG have no specific diagnostic value in relation to any single form of psychiatric disorder. It seems, on the contrary, that the more highly selected a population the fewer people with abnormal EEGs it contains (Williams, 1941c). The dysrhythmia appears to be a reflection of a defect which may have expression in one of many disorders, ranging from simple inadequacy, neurosis, or mild psychopathic behaviour, to epilepsy or even schizophrenia. The dysrhythmia may even be associated with normal behaviour or with a psychiatric disorder in the subject's relatives.

It cannot therefore be urged too strongly that in psychiatry as well as neurology the EEG should never be considered

apart from its clinical context Silverman (1943) has demonstrated this clearly in criminals, for he has shown that even habitual criminals do not necessarily have an abnormal EEG The incidence of abnormal EEGs is relatively high

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¹ [BMB 637]

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² [BMB 11]

ON THE PLACE OF PHYSICAL TREATMENT IN PSYCHIATRY

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The missionary spirit, always prominent in what has been said and published in favour of psychological treatment, now likewise pervades many of the writings on physical treatment in psychiatry The missionary spirit can be of much value in therapeutics, and psychiatry can do with a good deal of it to combat the resigned or Micawberish ¹ inertia which sometimes overtakes doctors faced with the difficulties and uncertainties of treating the mentally ill But fervour, which is proper to the advocate rather than the judge, may distort the true answer to the question whether a new remedy can now be used with discrimination and fairly sure effect Fervour can even, innocently but dangerously, give the impression that a drastic form of treatment should be tried (when in fact it is unsuitable), because it may do some good and nothing else will so that even tepid supporters come to say, with Dr Johnson,² "my opinion of alterative medicine is not high, but *quid tentasse nocebit*? If it does harm or does no good, it may be omitted"

Common Features of Physical Treatments

"Drastic therapies"—the term applied collectively to these new physical methods of treatment by Strecker (1944)—too strongly imply risk to the patient and audacity in the

Note to foreign reader

¹ [Micawber the name of a character in *David Copperfield*, by Charles Dickens]

² [Dr Samuel Johnson (1709-1784) Lexicographer, writer, wit, and subject of Boswell's famous biography]

psychiatrist who uses them But it is hard to find a suitable word to characterize the new methods and distinguish them from established physical procedures in psychiatry, such as hydrotherapy, and the manifold uses of drugs—to produce continuous narcosis, allay excitement, replace a missing constituent of food or internal secretion, stimulate appetite, and combat syphilis and other infections It would seem that the introduction of malaria for dementia paralytica was the bridge between the two sorts of physical treatment, and that just as dementia paralytica was for Kraepelin the *vesania typica*, so malarial treatment showed the three typical features of these new methods—they are empirical and severe, they are not directed only at symptoms, and they are applicable to conditions previously thought malignant or hopeless

It is no fault in a therapeutic procedure that it should at first be empirical Time and experiment correct that, and the historical fact that these measures for treating mental illness were derived from mistaken observations and untenable theories does not exclude them from good company But they would be in better company still if they were rational and their mode of action understood it would then be possible to prescribe them for an individual with a greater confidence in the outcome So long as their *modus operandi* is obscure, they are likely to remain to an undue extent hit-or-miss

It has been said that some of these methods, so unhappily misnamed "shock treatment," have much in common with the cruel procedures of a less humane age, and may be judged as we would judge *praecipitatio in mare* (which Boerhaave

recommended), flogging or the whirling chair. This also is a misconceived view. It is not by their antecedents or the alleged motives of those who use them, that the efficacy of methods of treatment is appraised. These physical methods do not act entirely *tuto, cito, jucunde* but they are reasonably safe in experienced hands, they often effect improvement with remarkable swiftness, and modifications in procedure have made them tolerable or unremembered. That they are now reasonably safe might be disputed, but their complications and risk are scarcely greater than those of many surgical procedures of good repute.

They are not concerned with the alleviation of symptoms; they are more ambitious and radical. This separates them from many other physical methods used in psychiatry, yet they are not therefore to be regarded wholly as striking at the roots of the sickness, for in leucotomy, at any rate, a permanent impairment may be the deliberate means, and price, whereby the patient is delivered from the distress of mind which his symptoms seem to occasion him. Some of the symptoms persist after the operation, but these unexorcised delusions or obsessions no longer move him as they did before.

The third typical feature is that the methods are used for conditions in which the outlook was formerly black. This is true, but has been often grossly overstated. So grossly indeed, that an uninformed onlooker might suppose that few people had recovered from an attack of schizophrenia before insulin was introduced into its treatment, and that psychiatrists until then had acquiesced like powerless onlookers in the fated deterioration of almost all such patients. Some of the most eager champions of the new method had been among the scorers of energetic treatment on general lines, such as Adolf Meyer so wisely advocated. With the zeal of converts, they have often assumed that before the new and dramatic procedure was introduced there had everywhere been the same therapeutic nihilism as in their own minds or hospitals, and they call any recovery "spontaneous" which has not been brought about by the new methods.

Control of Results

It is evident that the true test of these methods has nothing to do with *a priori* criticism or prejudices, but lies in their efficacy when compared with other methods of treatment that are applied with equal devotion and thoroughness. How do they meet this test? It is impossible to give an unequivocal answer: competent investigators arrive at discrepant conclusions. Penrose (1943), for instance, analysed by an ingenious statistical method the results of treating 1,600 inpatients in Ontario mental hospitals by means of insulin-hypoglycaemia or convulsions. 1,042 of these patients had been diagnosed "schizophrenia". He found that the remission rate attributable to "shock therapy" was negligible for the schizophrenics, and that convulsant treatment was more effective than insulin. He says, "very little support is provided for the view, formerly widely held, that shock treatment has value in schizophrenia." The impeccable statistical handling of his data might seem to justify acceptance of his finding. But another careful statistical analysis of approximately the same number of schizophrenics, treated in New York State Hospitals (Ross & Malzberg 1939), showed just the opposite: the results of insulin treatment were about three times as satisfactory as those obtained in a control group of schizophrenics, and convulsant treatment had not yielded results even as good as those obtained in the control group, who had had neither insulin nor convulsions. The conscientious studies of Bond & Rivers (1942, 1944), which confirm the value of insulin treatment of schizophrenics, are similarly in sharp opposition to those of Gottlieb & Huston (1943), who found that insulin did not increase the chances of recovery or shorten the duration of illness, when the patients so treated were compared with another very similar group of schizophrenics treated by conservative methods.

Such flagrant contradictions cannot be dismissed summarily in favour of the majority view. The evidence put forward by the more critical writers is in several instances weighty and respectable. The need to take it fully into account is underlined by the unanimity with which all observers attest the efficacy of convulsant treatment for affective disorders of late middle life: clearly, where the benefits of a novel method are indubitable, resistance to it cannot cloak or obstruct recognition of its value. There are, it is true, dis-

putes about the value of convulsant treatment for other than involutional disorders, just as there are disputes about its propriety because it can cause cerebral damage, fractures and other complications (Critchley, 1943), but these are symptoms of the same difficulties as beset the just evaluation of insulin treatment in schizophrenia, or of frontal leucotomy. Leucotomy, however, is so obviously a palliative method and almost a counsel of despair, that the claims made for it by responsible observers are modest, and even diffident; it is only in deciding whether an otherwise intractable mental illness may in any particular instance be mitigated by this surgical damage, akin to an amputation, that there is room for controversy.

Inherent Difficulties of Assessment

The physical methods of treatment here considered suffer from a disability more prominent in psychiatry than in other branches of medicine. The human being is here the necessary subject of any therapeutic experiment, because the conditions of the illness that is to be treated cannot be found or deliberately produced in animals. Consequently there are severe restrictions on the plan of the experiment, and especially on the choice of subjects and controls, the impartial observation of the results, and the study of the *modus operandi*. If the treatment is a mutilating one, as leucotomy is, it cannot be tried at first on any but hopeless cases (in many of which other methods of treatment will already have done their best and worst), and only an unequivocal result can safely be regarded as significant. This problem is not unknown in surgery and other branches of medicine, but it is more difficult to try a heroic treatment on patients such as those of the psychiatrist, who cannot themselves weigh its risks or advantages before consenting to it, and who are committed in a special way to the doctor's care for the very reason that they cannot be left to decide all their activities freely for themselves.

The chief reasons, however, why ten years after the introduction of a new method we are still uncertain about its range and effect are to be found in the complexity and nature of psychiatric data. The detection of a particular illness and the measurement of its severity at different stages of its course can hardly be carried out with that precision which would warrant the pooling of estimates about diagnosis and improvement by different workers. The less experienced and skilled the psychiatrist, the more likely that his criteria of say, schizophrenia, will occasionally diverge from those of his colleague, and that he will regard as proof of improvement or deterioration what another would call merely a change of form without prognostic significance. Hence the complaint of Ross & Malzberg (1939) and those working with them in the New York State Hospitals (Ross, Rossman, Clive, Schworer & Malzberg, 1941) that "different terms are used to describe the same conditions and different meanings given to the same term".

Awareness of the same difficulty led Malamud & Render (1939) to require that any author giving a report on the course of schizophrenia should specify the criteria he had used in diagnosis, but such specification would not tell much, nor would it safeguard the uniformity of classification. Course and prognosis are especially hard to evaluate on a uniform basis, even when diagnostic standards and methods are settled. Consequently a writer who compares the recovery-rate in his hospital after "shock" treatment with a much lower recovery-rate previously, may give as the "shock-produced" recovery-rate one that is no higher than that reported by doctors in other hospitals for patients with similar illness treated by conservative methods, yet it would be dangerous to conclude that he is not getting better results with his new methods.

Following up cases on a sufficient scale is notoriously difficult, and the assumption that patients enjoying a partial remission, who have remained in the community, are in better mental health than those in the mental hospital may be deceptive.

Need for Collective Investigation

Most serious of all the difficulties is the common lack of a co-ordinated plan for the therapeutic experiment. Small series of cases cannot furnish a decisive answer by themselves, and the findings from them cannot be pooled with those from other small series which may have been collected under materially different conditions. An organized experiment

would demand much that has not hitherto been practicable, including the voluntary acceptance by independent hospitals and clinics of an agreed procedure for the selection, management, evaluation of the mental state, and follow-up investigation of treated, as well as of control, cases. Such an experiment, as R. A. Fisher (1942) has demonstrated, requires much forethought, and self-discipline on the part of those who carry it out. It would not of course preclude individual experiments and tentative modifications of therapeutic method, but it would have to be conducted independently of them, itself adhering consistently to the agreed technique.

It has been noteworthy that, in the literature of "shock therapy," the majority of reports published on outcome have been premature or incomplete. Thus Ebaugh & Rymer (1942) found that among 50 papers which appeared between 1936 and 1942, 33 dealt with the results in less than 100 cases "and are markedly optimistic on the basis of a small series." Such papers have darkened counsel so far as efficiency of the treatment was concerned, even though in other respects they provided interesting and valuable data. They are to a considerable degree responsible for the needlessly wide swing of the pendulum of appraisal during the last decade.

The situation that has thus developed in the evaluation of some physical methods of treatment is by no means new in psychiatry. Similar difficulties hindered the steady healthy growth of psychological methods of treatment. It cannot even now be said that there is a consensus of testimony and opinion regarding the therapeutic value and the field of application of Freudian psycho-analysis, though it has been in use for nearly half a century. Like some of the physical methods, it demands very skilled administrators and can therefore be used on only a restricted number of cases. The choice of cases varies according to the judgment of the psychotherapist or the accidents which determine what patients seek his help. Technique varies from therapist to therapist, records are not kept on any systematic plan, and impartial assessment of the outcome of treatment is often hard to obtain. There can be little question that psychiatry, because of the extreme complexity and variability of its material, needs for its therapeutic trials an even more carefully devised design than does, say, wound-surgery or some branch of internal medicine. There can also be little question that the execution of any such project for a well-designed therapeutic experiment in psychiatry will meet formidable obstacles. These obstacles, however, should not be insuperable. It is only when the good results of a new treatment are unmistakable, because they appear with regularity or because they operate on a disease with a uniformly bad prognosis, that the need for an organized trial can be to some extent dispensed with. For the most important psychiatric conditions, such trials are essential, unless we are prepared to go on taking decades to decide questions which could be settled in a few years.

Collateral Problems

In all this it is only efficacy of the new methods of treatment that has been considered. There are many other aspects—the conditions which seem to favour the development

of new methods, the influence of such methods on the general theory of psychiatry and the outlook of psychiatrists—their physiological and psychological *modus operandi*, their complications and mortality, the technique, contra-indications, and trends, the modified versions introduced from time to time, the relationship to other, concurrent, methods, the medico-legal problems raised, and their bearing on problems not specially psychiatric (such as the effects of interference in the frontal lobes, or the bodily changes in extreme hypoglycaemia). These are questions of great amplitude—some of them are much discussed, and sometimes elucidated, in the voluminous literature, others are urgent in their practical importance, as they are now involved in the methods by which psychiatric disorders in members of the Armed Forces of the United Nations are either treated or averted. But it would call for much fuller consideration than is here practicable, if these questions were to be examined. The recent exposition by Sargant & Slater (1944) deals with many of them, as did Jessner & Ryan's manual (1941) four years ago. Cook (1944), Tennent (1944) and Fleming (1944) have lately reviewed the literature critically, and (though the stream has become in the last three years less profuse and less turbid) there is still a flow of articles reporting and surveying the varied problems.

Conclusions

There are many physical methods used in psychiatry besides the induction of convulsions, insulin coma and frontal leucotomy. Continuous sleep, artificial pyrexia by malaria and other means, tryparsamide administration, hydrotherapy, "narcotherapy" and the exhibition of various endocrine and vitamin preparations, have been employed, and lately, for a short time refrigeration also. Many combinations too have been essayed—artificial pyrexia and fits in the treatment of schizophrenia, for instance, and insulin after malaria, for dementia paralytica. These three, however—insulin, fits, and leucotomy—illustrate the difficulties and problems that must be faced when any treatment of a psychiatric illness that is without demonstrable somatic pathology, has to be appraised. The problems are still there, even after one has agreed that convulsions are almost specific for involutional melancholia, that insulin often shortens the duration of an attack of schizophrenia and prolongs the subsequent period of satisfactory mental health, and that leucotomy may make life in the general community possible and even outwardly normal for an agitated or tormented patient who would otherwise have to spend the rest of his lifetime in a mental hospital.

The indications, the mode of action, the risks and limitations of these methods, are still too much a matter of statistical statement about groups rather than of precise statement about the individual to be treated. Similar uncertainty, it is true, prevails regarding the treatment of some physical diseases of perhaps equal gravity and prevalence—but the rightful pretensions of psychiatry and the advances it has been able to make in treatment during the present century warrant an impatience that cannot be allayed by noticing that other branches of medicine are in much the same predicament.

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THE PRESENT POSITION OF PSYCHOLOGICAL RESEARCH IN BRITAIN

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Psychology apart from psychiatry, has now become a subject with many ramifications. These include intelligence-testing, vocational guidance, social psychology, animal psychology, job-analysis, motion study, work on special senses (such as

hearing and vision), learning, temperament, and so forth. It also tries to bridge the gaps between other subjects such as physiology, medicine and engineering. For instance psychologists have been called in, especially in war-time, to assess

the effect of discomfort and heat and cold upon performance of mental tasks, to assist in the design of gun- and machine-controls which must be operated manually with the greatest accuracy and the least fatigue, and in the design of instrument-lighting for aircraft and tanks to ensure legibility of the instruments with the least dazzle and the least impairment of night-vision. They have also been asked to assist in the design of clinical medical experiments, so as to minimize the effects of suggestion, practice, boredom or fatigue in experiments on vitamins and other substances. In peace-time, the Cambridge Psychological Laboratory was largely concerned with work on animal and human learning, and on visual and auditory perception, mainly by the study of these senses in human subjects, but sometimes aided by electrical recording of nerve impulses in animals and by other physiological methods.

Formation of a Psychological Research Unit

Apart from Cambridge, most British peace-time research in psychology tended to be on selection tests, vocational guidance, and educational and social aspects. In these circumstances, many of the psychologists from other universities have entered, or been consulted by, the military services, while the more purely experimental and physiological problems have been mainly investigated by workers who are, or have been, at the Cambridge Laboratory. Thus Zangwill and Paterson, now in the Brain Injuries Unit, directed by Mr Norman Dott at Edinburgh, have done much work on devising objective tests for the visual perception, verbal comprehension, and mechanical and arithmetical ability of patients suffering from brain injuries, both with a view to diagnosis and prognosis as to the advisability of operation and the degree of recovery to be expected. Several of the workers at present at Cambridge were employed by the Medical Research Council, under the direction of Professor F C Bartlett. In the spring of 1944 they were formed into the Medical Research Council Applied Psychology Research Unit, of which Professor Bartlett continues to have general supervision. At present this Unit consists of 14 research workers—four graduates in medicine, the rest graduates in physiology, psychology or natural sciences.

Until the work of the military services on selection testing becomes public, it is difficult to forecast progress on these lines, except that it is clear that the availability of very large numbers of subjects to be tested, and of follow-up facilities, has given a great impetus to this branch of applied psychology, and that the type of personnel required for giving tests and doing the subsequent statistical work will be well understood.

Problems Studied by the Research Unit

The type of psychology with which we have been mainly concerned has necessarily involved problems largely of an *ad hoc* character, undertaken in response to requests from military departments, but certain common principles have emerged, which may assist in guiding a fruitful approach to future and peace-time problems. These principles are those of suiting the job to the man, of suiting the man to the job, and of improving the man's performance.

The first involves mainly the design of instruments, machinery, layout and illumination of maps, panels, etc. These problems may be broadly divided into those of *display* and *control*. The first term is that used by military scientific departments to cover the methods by which information is laid visually before any operator, whether on a map, a graph, a cathode-ray tube or an instrument panel. Often the best type of display is a compromise, e.g. between an instrument-panel so complex that its interpretation is slow, or so simple that it gives insufficient information, or (in the case of a night-fighter aircraft panel) so brightly lit that it dazzles the pilot or so dim that it cannot be read. Psychological experiments, employing laboratory simulations of the real conditions, often enable the optimum type of display to be decided upon. Even where an optimum does not exist a graph of the relation between, for example, the distance of a plotter from a map and his accuracy in reading grid references will show a very steep rise in error beyond a certain point, and thus indicate a definite practical limit to the viewing distance, as in certain work by Dr Mackworth. Display problems are also relevant to decisions and policy in industry and planning of all kinds, for the correctness of these decisions may depend very largely on the clearness with which the

relevant information has been presented to the responsible person, in the form of verbal statements, graphs, records, or tables of figures. There should be a great deal of scope for such work in peace-time industrial design, especially in ensuring easier operation and preventing accidents, e.g. in instrument panels, indicators, information charts and graphs.

General principles have emerged which narrow the field for *ad hoc* experiments. Exact methods of scoring efficiency in war-tasks, such as watch keeping, which are of a boring but responsible nature, have shown ways of determining optimal periods of work. The effect of discomfort, fatigue and noise on such tasks is also being studied. These techniques for the measurement of human abilities may eventually provide useful ways of assessing the progress of patients recovering from physical or mental illness, and perhaps may also test innovations introduced by researches in preventive medicine.

On the motor side, the positions, forces and gear-ratios of handles and levers on guns and machine tools are usually compromises between the factors of speed and precision of operation, of simplicity and mechanical perfection, or of psychological and physiological suitability. Here again, particular cases are being dealt with by laboratory simulations with exact scoring of performance, and interesting principles of muscular action and sensory-motor co-ordination are emerging. These studies verge on both physiology and preventive medicine.

Fitting the Job to the Man

There are similar problems in industrial design (such as the hand-wheels on a machine-tool, the stage at which servo-motor or remote control becomes necessary, and the most suitable form for such control) while general principles of use to designers in less important cases could be formulated. Industrial accidents very often occur in the holding or manipulation of materials. Thus, the material may be thrown against the operator or may crush his limbs when circular saws, grinders or portable drills are being used, or he may be cut by burrs and sharp edges, or injured by a press or mulling machine when he is fixing work in position. It would seem that the flexibility of modern engineering methods, such as magnetic chucks, remote-controlled pneumatic chucks, etc., should do much to reduce such accidents, and that psychologists can point out where such devices are needed and consider whether certain designs of them will be acceptable to the worker.

Any human act can be regarded as the result of a sensory-mental-motor chain of events, and hitherto those in the Unit who have worked on the above problems have concentrated rather on the sensory and motor ends of this chain, partly because of their individual aptitudes and partly because these are the most fruitful sites for instrumental modification. There is probably, however, an interesting future field in the analysis of the factors that make a task intellectually difficult, and that have led industrialists to division of labour, with its advantages of increased output and its disadvantages of boredom and discontent.

This approach—suing the job to the man—should, we feel, be explored to the full, as it puts the industrial jobs necessary for improved standards of living within the power of the majority, whereas psychological selection alone, especially when the job has been made unnecessarily difficult, may result in a high rate of rejection and unemployment.

Fitting the Man to the Job

There is, however, need for *allocation* of the available workers so that they are given tasks for which they are suited, and some selection where a task is unavoidably difficult. This second approach—suing the man to the job—is principally being tackled by a team under Dr Heim. They are members of the Unit but are working on behalf of the Industrial Health Research Board of the Medical Research Council. They have devised a battery of tests and standardized it on a large number of entrants to factories and Government Training Centres and some university undergraduates and are obtaining follow-ups on the industrial subjects. This battery contains a paper test (AH4) consisting of a verbal and arithmetical and a visual part, based on relations of identity and opposition, analogy, completing series and following instructions, a mechanical ability test and an inspection test consisting of metal blocks containing small

defects, performance being scored on an accuracy index, speed also being recorded, some other performance tests resembling factory gauging- and assembly-tasks, and the National Institute of Industrial Psychology Form Relations test. The emphasis of such work must necessarily be on individual differences in ability, rather than on the features of a task which make it difficult to all men.

Research is being carried out on consistency and validity of test results and of assessments, and on the relation between these two criteria. The extent to which the value of a test depends on its degree of analogousness, and the distinction between differences of grade and type of ability, are also being studied.

Other members are investigating night-vision and other tests from the point of view of selection and of diagnosing vitamin-deficiency and disease. It is hoped that there will also be some time for fundamental work on the special senses. Mr Farmer has begun a study of the capacities of blinded officers with a view to their obtaining suitable employment. Others are using methods which link almost equally with both of the two main approaches discussed above. For instance, Miss Vernon is working on visual-form perception and memory, with a view both to lay-out of visual tasks and the allocation of personnel, and Dr Davis on the sensory motor co-ordination and responses of temperamentally different types of people in controlling machinery.

Improving Performance

The third main approach is to improve the performance of the man, either by nutritional means or by mental and physical training. This, again, involves carefully controlled experimental tests of sensory and motor efficiency and scoring of performance. Various synthetic training devices have also been produced for military use. Similar devices may well have a peacetime application, e.g. to motor-driving or machine-tool operation, where the novice is apt to injure either himself or the machine and to gain little insight into what he is doing wrong. Synthetic training equipment with exact scoring devices can assist here, but psychological experiments should always be undertaken to see whether any trainer is in fact saving training time and improving performance, and whether the equipment would be equally useful if it were simplified, or very much better if it were slightly complicated.

Statistical Treatment of Findings

All these lines of approach involve much statistical work—for example, to establish the significance of the optimum values found for some feature of instrument design, and to reveal the consistency or inconsistency of an allocation test, and its validity as judged by follow-up evidence. Though most of the members do the simpler statistical treatment of their own results, Mr Chambers and Mr Whitfield help in applying more complicated methods and in the development of new ones. Mr Whitfield is also instituting a new type of recording system in a group of coal-mines and two factories, with a view to tracing causes of absenteeism, sickness and accidents. Such investigations give indications of definite fields for experimental research into improved equipment or of the need for re-allocation or retraining of accident-prone workers.

The Direction of Future Work

It is hoped that there will be close contact with other bodies undertaking similar work—for instance the National Institute of Industrial Psychology—and with personnel managers, safety-officers and medical officers in factories. While the Unit will always be very glad to hear of any problems which appear to come within its scope, it must be emphasized that it is primarily a research body and has not the personnel nor the time available for investigations of purely specific and local interest. Thus Dr Heim has introduced, in several factories

for which she has worked, a scheme by which members of her team inspect the problem and decide what existing test would seem appropriate and develop new tests if necessary, the firm then provides a suitable person who is trained for a fortnight or so at Cambridge and returns to the firm to give the tests and forwards the results at intervals to Cambridge. Similarly, it will be impossible to take on a large number of particular problems in display or control design, but wherever a problem of wide interest arises, or one involving test-methods which could be routinely applied elsewhere when they had been developed, the Unit is very anxious to be of assistance. It is hoped that similar work may continue for the military services in regard to their more fundamental problems. The essential thing is that the scientific abilities of the members for basic research which ought, sooner or later, to have its effect on particular problems, should not be swamped by work of transitory and local value.

It is also to be hoped that there will be time for more fundamental work on the special senses and on muscular movement. At the present time, some fascinating problems in these fields are beginning to reveal themselves. On the one hand, the great advances in electronic technique (i.e. valve amplifiers and oscillographs) just before and during the war should greatly increase the scope of nerve and muscle action-potential recording, and so permit closer correlation between psychological experiments on sensation and physiological experiments on the sensory pathways, such as those of Granit in Sweden, using microelectrodes, Hartline in America, and Adrian in Cambridge. On the other hand, electronic technology has recently added to man's own sense-organs artificial "sensory devices" such as Radar,¹ and artificial sensory-motor systems such as robot pilots for aircraft and other servomechanisms. The engineers who have designed these often seek to apply the same theory to the human operator in, for instance, flying an aircraft, and although the human being's behaviour is more flexible, more variable, and as a result less exactly predictable, the analogy has been an extremely illuminating one to the psychologists and physiologists who have been consulted. It suggests many interesting lines of approach to the problems of self-regulating systems in the body, such as temperature-regulation, where all types of physiological response are involved, from an unconscious neural adjustment such as vasoconstriction or sweating, up to a high-level learned response such as putting on more clothing or closing the window.

The designer of "servomechanisms"—of which robot-pilots and thermostats are examples—regards such a system as one which automatically compensates itself for external disturbances and maintains the required state of equilibrium. Similarly we may regard a human being as having to maintain himself in a state of equilibrium with his environment, as regards temperature, blood-oxygen level, cell nutrition and in other ways. On the analogy of a servomechanism this implies that any disturbance of the equilibrium-state must cause some sense-organ to send nerve-impulses to the central nervous system where they evoke a compensating reaction, either by an unalterable reflex pathway or by a modifiable or learned one. So great is our ignorance of these physiological mechanisms—for instance of why we "want" to eat more when our cell nutrition is in danger of becoming impaired—that they have often been regarded as completely outside the realm of physical and physiological explanation. For instance, J. S. Haldane considered that when the respiration-rate and -depth of an organism was regulated by its energy requirements, some new and vital principle must be invoked. Yet the existence of artificial devices which are self-governing in this way should stimulate the physiologists and psychologists to see whether they cannot find out more about the means by which the body maintains its state of equilibrium and of adaptation to its environment.

¹ [Radio apparatus for detecting the approach of aircraft, ships, etc.—Ed.]

REVIEW OF SELECTED PAPERS

Cerebral Mechanisms

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I. BRAIN RHYTHMS

by E. D. Adrian, *Nature*, 153, 360-362, 25/3/44

II. SENSORY AREAS OF THE BRAIN

by E. D. Adrian, *Lancet*, 2, 33-35, 10/7/43

III. LOCALIZATION IN THE CEREBRUM AND CEREBELLUM

by E. D. Adrian, *British Medical Journal*, 2, 137-140, 29/7/44

While it has been known for many years that characteristic electrical effects accompany nervous activity, their investigation in the central nervous system remained very limited until the advent of the valve amplifier. Some aspects of the progress it has made possible, and the scope and limitations of its application, are the subject of these three lectures by Professor Adrian.

In a Friday Evening Discourse (I) at the Royal Institution, Adrian reviews the progress that has followed Berger's report in 1929 of a uniform electrical pulsation in the brain which may be recorded through the intact skull and scalp. He discusses the relation of α activity to attention. α rhythm is a rhythm of inattention, a positive activity, which apparently fills those parts of the cortex which are for the moment unemployed. It is maximal not in areas where sensory messages are received but in neighbouring silent or association areas. It disappears when attention is turned to the visual field, returning when attention is diverted to other fields. It may, however, be abolished by concentrated mental effort, in which case the whole of the α area goes over to non-visual work. While probably the whole cortex determines whether α activity should continue, it appears that a relatively small central field, in the neighbourhood of the thalamus and near incoming pathways, balances conflicting claims and actually decides its spread.

As there is much ground for the view that there is a central area determining attention and the control of α activity, abnormalities of α rhythm might be expected where there is disturbance or abnormal control of attention. Viewed from this aspect, α activity becomes a feature of the constitution of the brain to be related to personality. While the diagnostic significance of the electroencephalogram in personality disorders is yet poor, a notable advance has been made in the relating of behaviour to a measurable feature, though gross, of the electrical activity of the central nervous system.

Consideration of the mechanism of the afferent areas suggests that experience and behaviour are to be related more precisely to patterns of nervous activity. This view is presented in two other lectures, the Sharpey-Schäfer memorial lecture (II) to the Faculty of Medicine of Edinburgh University, and the Bertram Louis Abrahams lecture (III) to the Royal College of Physicians, in which Professor Adrian deals with localization in the cerebrum and cerebellum. In the case of the cerebellum, knowledge of function had been confined to the clinical findings until the new electrical methods gave some evidence of localization. They have shown the error of schemes based entirely on morphological grounds, and disclosed differences in representation in different species, but as yet they have not elucidated the problem of the large fraction of the cerebellum which does not appear to be employed in any localized representation of the body and limbs. One of Professor Adrian's (1943a) own contributions to the study of the cerebellum is best reviewed separately.

Progress in the application of electrical techniques to the sensory function of the cerebrum has been rapid. They have given a valuable check on the position of the afferent projection areas of the cortex, hitherto derived chiefly from histological and clinical findings and animal ablation experiments. Thus the striate projections of visual afferents have been mapped accurately for all parts of the retina (Talbot & Marshall, 1941). The arrangement in the cortex is found always to bear a simple relationship to that in the eye. In different animals the proportions vary, for instance in the monkey a large part of the cortical area is connected with the macula and very little with the periphery. As well as a spatial pattern, a temporal pattern may be discerned

as in the reproduction in man, in suitable circumstances, of rates of flicker. The retinal messages may spread widely, impressing their rhythm on some of the association areas. This flicker area may sometimes amount to about a quarter of the area of the α rhythm.

The projection of sound afferents in the auditory cortex has been investigated by Woolsey & Walzl (1941) and Licklider & Kryter (1942). In the cat and monkey the apex of the cochlea supplies the antero-lateral, and the basal turn supplies the postero-medial part of the superior temporal gyrus. Thus, an up-and-down note will cause activity oscillating to and fro in the cortex of Heschl's gyrus. In man, the auditory area is much smaller than the visual, and its activities are extremely difficult to detect through the unopened skull. But the same oscillation may reasonably be expected. Galambos & Davis (1943) showed, in an analysis of activity in single fibres of the auditory nerve, that each fibre came from receptors tuned to a particular pitch, but was capable of reacting to louder notes of pitch not far different. The auditory fibres behave in every important respect like other sensory fibres. The message conveyed is not itself marked by any particular frequency. It is distinguished from other nerve messages only by its source and destination.

For smell there is less direct evidence, but it is highly probable that distinctions of sensation are based on differences of pattern in the olfactory cortex.

Many findings suggest that the cortex deals only with selected information. Even in barbiturate anaesthesia, which is commonly used for these experiments and gives conditions which eliminate interaction of neurones at synaptic levels, there is much modification of the messages sent to the cortex. There is a good deal of distortion or "editing" as Adrian would describe it. Comparative studies emphasize the selected nature of the data used by the brain. It requires information for the modification of behaviour, but clearly the wants in different animals are different. Adrian has strikingly illustrated the relation of brain representation to body structure and habits. Thus in the hoofed animals the limbs are used almost entirely for semi-automatic movements of locomotion and little information from them reaches the cerebrum. In the carnivora the brain records, it would seem, a fairly detailed picture of most of the exposed parts of the body. This is necessary for movement in the search, hunt and capture of prey. The position in the ungulates is reviewed elsewhere (Adrian, 1943b) in greater detail.

It is clear that, as yet, workers with electrical techniques have uncovered only the first link in the cortical chain of events which correspond to sensation, perception, association and appropriate action. The very method of barbiturate anaesthesia is designed to simplify the picture of the arrival of sensory messages. The picture in the normal un-anaesthetized brain is practically unknown. The nearest approach to the recording of the nervous basis of perception is found in the simple demonstration of a change in the rhythm of electrical waves of the occipital area which coincides with a change in the subjective impression of rates of flicker. For the investigation of the consecutive interactions, which determine the interpretation of sensory messages and behavioural response, possibly entirely new methods may be required.

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¹ [BMB 618]

² [BMB 617]

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AFFERENT AREAS IN THE BRAIN OF UNGULATES

by E. D. Adrian, *Brain*, 66, 89-103, June 1943

Recently Professor Adrian (1941) has compared the chief regions of the body which send information to the cortex in

the rabbit, cat, dog and monkey His method is to record the electrical activity of the cortex evoked by touch and pressure In extending observations to the ungulates he has disclosed differences in the somatic receptive areas of the cortex which may be related to the life-habits of the particular animals considered

For the examination of the electrical activity of the cortex, the animals were anaesthetized with allobarbitone Potential-changes were amplified and converted to sound It should be noted that when an animal is deeply anaesthetized by the barbiturates, the activity in response to cutaneous stimuli is strictly localized Under light anaesthesia or under chloralose more widespread effects may follow In the particular method used, the receptive areas disclosed are those to which afferent impulses are sent by the direct routes They are smaller than the "sensory areas" as defined by Dusser de Barenne's method

It was found that in the goat and sheep the chief supply to the cortex comes from the upper and lower lips on the same side The fore-foot and sometimes the hind-foot send discharges to an area of the contralateral ectosylvian gyrus, caudal to the face area Findings in the pig are in contrast No discharges from the limbs or trunk are detected and the whole of the cortical area is taken up by the representation of the contralateral snout, on a scale which suggests that the tactile discrimination of the pig's snout should be as great as that of the human hand In the small horses examined (Shetland ponies) the position of the receiving area resembles that in the sheep and goat but it represents mainly the opposite nostril

A reason for the arrival of impulses from the face area at the same side of the brain in the sheep and goat and their crossing to the opposite side of the brain in the pig and horse is suggested by the relative dominance of the visual and olfactory apparatus In the leisurely feeding of the sheep and goat, smell is likely to be an important guide until the food reaches the lips, tactile function of the bare nostril is limited and concerned mainly with feeding, what representation it has in the brain is thus likely to be coupled with the olfactory rather than the visual patterns In the rodents and carnivora, tactile and visual impressions are integrated and determine the motor agility of the hunting animal So, too, in the pig the tactile impressions of the snout are important in digging Tactile and visual messages are related, the tactile afferents crossing In the horse, messages from the hairy nostril have a broad representation in the cortex, the nostril being the chief part of the body to be used in tactile exploration, and as they call for amplification on the visual rather than the olfactory apparatus, it seems reasonable that they should cross to the appropriate hemisphere These, of course, are but suggestions, and their acceptance must await a greater knowledge of the roles of sight and smell in animals than is available at present

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AFFERENT AREAS IN THE CEREBELLUM CONNECTED WITH THE LIMBS

by E D Adrian, *Brain*, 66, 289-315, December 1943

In mapping the afferent areas of the cerebellum, Dow (1942) applied electrical stimulation to the afferent pathways Professor Adrian in the present work has used the stimulation naturally derived from touch, pressure, movements of joints, stretching of muscles, and pulling of vibrissae Using this method on a large number of cats and monkeys he comes in general to a similar localization, but is able considerably to amplify previous findings adding much detail about the particular connections of different parts of the body Observations were also made on dogs and a goat

In the cat and monkey, spinocerebellar discharges from the hind-limb appear in the lobulus centralis on the same side, and behind them in order are discharges from the forelimb in the culmen and from the vibrissae of the snout in the lobulus simplex This afferent arrangement is the opposite of the efferent arrangement shown by Connor & German (1941) in ablation-experiments in dogs, cats and monkeys When the culmen was excised Connor found defective control over the hind-limbs, and, when the excision was further

forward, symptoms were in the fore-limbs Without more experimental evidence it is idle to speculate on the nature of the co-ordination mechanism based on an arrangement of afferent and efferent connections which appears so anomalous

Single unit discharges in the cerebellum may be picked up by a wire electrode with its tip 1.5 mm or more below the surface They are found to differ little from the activity shown in peripheral nerve fibres The commonest are from pressure receptors in the feet and receptors in joints and muscles Some convergence of pathways from the periphery is indicated by the finding that a single cerebellar axon may be in contact with a much larger receptive field than the peripheral nerve fibre

Pontocerebellar connections were examined in detail in monkeys by observations of the effects of the discharges evoked by electrical stimulation of the motor cortex or by the application of strychnine Pontocerebellar discharges in the lobulus centralis, culmen and lobulus simplex are derived from the hind-limb, fore-limb and face regions of the motor cortex The receiving areas overlap those for the spino cerebellar discharges, extending farther out laterally

The intrinsic activity of the cerebellar cortex and that of the cerebrum have features in common In periods of diminished rigidity, the intrinsic activity studied in the decerebrate preparation of the cerebellum appears as small potential waves of high frequency (150 to 250 per second), increased in size and speeded to about 300 per second on the arrival of afferent discharges The increase is greatest in the region of arrival but there is some spread of the effect so that a stimulus to the hind-foot may cause a slight increase in the activity of the fore-foot area (culmen) as well as a much larger increase in the lobulus centralis

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ON THE MODE OF REPRESENTATION OF MOVEMENTS IN THE MOTOR CORTEX WITH SPECIAL REFERENCE TO "CONVULSIONS BEGINNING UNILATERALLY" (JACKSON)

by F M R Walshe, *Brain*, 66, 104-139, June 1943

Knowledge of the functions of the motor cortex has been derived partly from clinical observation and electrical stimulation of the human cortex and partly from experimental stimulation and ablation in animals Before 1870 it was thought that the cortex was inexcitable and that no localization of function existed Lesions were believed to produce only a general depression of function, except for the speech disturbance, which occurred with lesions of the posterior part of the left third frontal convolution These views were shown to be erroneous by the work of Jackson, Bastian and others

Clinically, there appear to be three predominant foci in the motor cortex from which Jacksonian fits invariably arise These represent movements of the thumb and index, angle of the mouth, and the hallux Nearly all Jacksonian attacks seem to spread from these parts in an ordered "march" usually corresponding closely with the topographical order of localization of movements of the cortex as revealed by experimental stimulation Jackson called these three foci "physiological fulminates" They must have physiological properties not shared in equal degree by other regions of the cortex that lead them to react in this way

Jackson's hypothesis

Jackson pointed out that the cerebral cortex represents sensor-motor processes, performances and not performing parts, movements not muscles He believed that the motor cortex represented all the movements of which an individual is capable, implying a distinct and separate representation for innumerable movements Hence, those parts having the most numerous and varied movements must have the most extensive representation in respect of these movements, while parts having the fewest distinct movements need a correspondingly limited representation In order of importance, the leading parts are the thumb and index, lower part of the face and the foot The extensive representation that these

movements require, with the numerous patterns of excitation underlying them, necessarily involve correspondingly extensive anatomical substrata, nerve cells, fibres and connections. Increase in differentiation is attended or followed by more complete integration, which is far-reaching. It is exemplified by the act of lifting a heavy object with the hand. The muscles moving the hand and digits move into the posture for grasping the object, the wrist fixes the hand, the arm directs it to the object and in turn the muscles of shoulder, trunk and lower limbs brace the subject's frame so that objects may be lifted. The movements proceed from the most voluntary to the most automatic.

Every act therefore involves the closest relationships between all parts of the motor cortex, incompatible with the conception of abrupt localization of movement. Hence the hand area, for example, is not merely the cortical region in which movement of the hand alone is represented, but one in which the movements are mainly and predominantly those of the hand. Conversely, this area is not the sole representation of hand movements, for these are represented subordinatedly throughout the motor cortex. Thus the motor cortex is to be considered not as a mosaic with abrupt localizations, but as a complex pattern of overlapping and graded representations. Following a local destructive lesion, the functions of the destroyed part are not taken over by other parts, and compensation is never complete, but the loss is virtually concealed by the repertoire of movement which remains intact. Such a planned representation implies that a stimulating lesion releases a widespread convulsion which is not necessarily associated with a spread of the excitatory processes in the cortex. All normal movements must involve wide fields of muscle, and none are narrowly confined to the muscles of a single part. In every normal movement-complex, one movement is the predominant component, but there are numerous subordinates.

Punctate localization theory

Electrical stimulation of the cortex presents a picture of a mosaic of excitable points, each yielding a characteristic and circumscribed motor response, such as a small movement or sequence of small movements employing small numbers of muscles. The response is often determined, however, by pre-current stimulation of the same or adjacent points and is thus inconstant. This instability of response was analysed by Leyton & Sherrington (1917), Graham Brown (1915a, 1915b, 1915c) and Graham Brown & Sherrington (1912) into three factors: facilitation, deviation, and reversal. Cortical stimulation experiments, e.g. those of Bubnoff & Heidenhain (1881), showed that if the stimulation is repeated at brief intervals there is an increase in the motor response evokable from that point, an antecedent cutaneous stimulation of the limb responding to cortical stimulation augments the responses. The excitability of adjacent cortical points is also increased by these processes (secondary facilitation). The same procedure may lead to an alteration (deviation) of the response previously obtained from a point adjacent to that which is being stimulated recurrently. Thus, after stimulation of successive regions of the arm- and hand-area, the hand-area may overlap that of the face, where previous stimulation had not produced movements of the hand. Facilitation may be demonstrated not only within a given functional area, but from one functional area to another, e.g., arm to leg.

In other cases, when an initial stimulus to a cortical point is repeated after an interval of one or more seconds according to circumstances, the second stimulus can produce either a diminished or no response (extinction) (Dusser de Barenne & McCulloch, 1934, 1939). Dusser de Barenne, Garol & McCulloch (1941) have recently claimed that, under the influence of secondary facilitation, motor responses may be obtained from a wider area of cortex, both pre- and post-central, than indicated in the work of Leyton & Sherrington (1917). Bounding this area anteriorly and also within it, they report the presence of four zones of cortex running coronally from vertex laterally, stimulation of which inhibits the normal electrical activity of the cortex and also the appearance of motor responses from normally excitable areas.

Cortical stimulation reveals fragmentary reactions and not the general design of the movements represented at that point. It "samples" the motor cortex. Whether such an abnormal stimulus as an electric current can be considered as producing stimulation of normal function in the motor cortex is doubtful,

but it is on this foundation of discrete representation of small items of movement, each highly co-ordinated with others yet separately elicitable, that Leyton and Sherrington developed their view of the function of the motor cortex. Such individual movements are elicited from minutely localized stimulation, and each movement is a fraction of some more complex act which would involve combinations of these unitary movements to make up a useful whole. Different movements are produced by different combinations of these motor units. Facilitation and deviation of response indicate that the building up of these movements is a main cortical function. However, these phenomena tend to indicate an instability difficult to explain on this hypothesis. The obscurity is revealed by the statement that the fixity of motor localization as regards minutiae is to some extent probably a temporary one, possibly varying with different conditions. Deviation is not explained in this theory, and in itself implies that there are really no fixed foci of localization of units of movement in the cortex.

Synthesis of two hypotheses

Jackson realized that the notion of the localization of a single unit of movement in a single cortical point is not in accord with the facts of clinical and experimental observation. There is more physiologically in a single point than a single movement. Once this is accepted, the difficulties and inadequacy of the punctate localization theory vanish, and facilitation and deviation are of greater significance. On Jackson's hypothesis, the variations in motor response of a given cortical point from moment to moment no longer require the supposition that localization changes in space in the improbable manner hitherto assumed. They can be fully explained by changes in the relative thresholds of excitability of the different patterns of excitation (different representations) localized in a given cortical point under the influence of facilitation.

The view that the movements of any given part are widely represented throughout the motor cortex, but maximally at a focus, implies that movements of this part are more abundantly represented at this focus than are other movements. At this point there is a grading of localization, and movements of that particular part have the lowest threshold of excitability, or are the predominant pattern of excitation, and they appear therefore as the primary movements on brief electrical stimulation. The fact, however, that even in these circumstances secondary, tertiary, and other movements may follow the primary movements in sequence, suggests the presence at that point of multiple representation of varying thresholds. It has long been known that isolation of a cortical point by cutting round it does not prevent spread of an epileptiform convulsion evoked by electrical stimulation of that point. Also the division of the corpus callosum does not prevent this spread from involving the muscles of the same half of the body.

The latter observation is in accord with Jackson's view that discharge from a single motor cortex may evoke bilateral convulsion. Jackson's hypothesis is that the motor cortex represents the normal movements of the individual as seen under normal conditions. In the case of what he calls the leading parts, e.g. the hand with a great repertoire of complex movements and the widespread subordinate movements associated with it, extensive fields of cortex are involved and overlap and are interwoven. Within such a field there is a focus mainly concerned with hand movements, the patterns of excitation laid down in learning movements being mainly represented here. The function of this focus is predominantly, but not exclusively, to initiate hand movement, and these are the primary movements revealed by the "sample" of the electrical stimulus and those first activated in normal conditions of cortical activity, but as parts of other patterns of excitation are also present here, we get a secondary and tertiary response to electrical stimulation—movements of other parts normally associated with hand movements. Passing from this focus, regions of cortex are reached in which the foci of movement of other leading parts are situated. This means that at any point in the motor cortex the neurones form the substrata of numerous patterns of excitation, but one pattern predominates.

If by appropriate antecedent local stimulation, the focus of thumb-index movements is facilitated by lowering their threshold of excitability, a corresponding depression of excitability of the other patterns of excitation represented there

must ensue, and the areas over which thumb-index movements may be evoked will be increased. Thumb-index movements will now appear as primary movements from points in which, before facilitation, other movements were evoked as primary movements. It is not, as the punctate theory supposes, that the relation between cortical focus and peripheral muscles has been broken down, but that the relative threshold values of the different patterns have changed. The localization of movements in the cortex does not change spatially, but there is merely a changed excitability leading to deviation of response. Deviation of response regarded in this way is not a phenomenon in the same category as facilitation—which is a fundamental neural process—but simply one of three possible consequences of facilitation, the other two being augmentation and reversal of response.

Jackson differentiated co-ordination into two elements, spatial and temporal. The plan already considered provides the anatomical substratum of co-ordination in space. Co-ordination in time deals with the "order of action" of movements—that is, the sequence of movements when a motile part such as the upper limb is in action, as in lifting a heavy weight. It is relatively fixed, the leading parts coming into action first, followed by the automatic movements. Thus representation of movement may be said to have anatomical and physiological aspects—the cortical field and the order of action respectively. Facilitation is a primary factor in determining this order of action or co-ordination in time. Under normal conditions of activity, the excitable motor cortex is activated by the higher-level mechanisms in the frontal lobe, and facilitation is probably a process of importance in this activation. Co-ordination in time is of importance in the behaviour of the convulsions beginning unilaterally where there is not a normal sequence of movement but all occurs simultaneously. A convulsion may be rightly described as a disorder of co-ordination in time. The idea, according to the punctate theory, that co-ordination in space and the building up of a movement-complex occur by simple summation of units of movement is unnecessary if Jackson's view, that each normal acquired movement has its own special representation, is accepted. If when some skilled movement is carried out it is built up from unit components, the learning of such a movement must involve the laying down in the cortex of some permanent trace, and this is merely another way of saying that the movement is represented in the cortex in its natural and complete form. Probably, therefore, such a group of finely complex movements as those engaged in speech are in fact represented as such in the cortex.

The fact that local lesions of the motor cortex do not produce complete palsies of particular movements, but that restoration of a motor function can occur in part, cannot be explained on a basis of punctate theory, but follows naturally from Jackson's postulates. Thus ablation of the hand-area still leaves intact numerous subordinate representations, which compensate partly for the loss of primary representation. Walshe concludes that, on the evidence available, Jackson's ideas on the mode of representation in the motor cortex are correct, and that moving parts must have wide representation in the cortex. Even a brief minimal faradization commonly evokes secondary movements in consequence, as revealed by the findings of Leyton and Sherrington.

Characteristics of convulsions beginning unilaterally

The author employs Mercier's (1881) scheme of the musculature dividing the muscles into series. A limb-series stretches from apex to base, the highest members being distal and the lowest proximal. In the upper limb the highest members are the smallest muscles, which also have the most numerous and special movements. The lowest members are the largest, with the simplest and smallest range of separate movement. In the head and neck, the muscles of the eyelids and round the mouth are the highest, and those of the neck the lowest, of the series. The lowest members of all the series are the muscles usually employed in bilateral movements. The convulsions beginning unilaterally are now considered from the point of view of the following:

i *Focus of onset* Usually the fit begins in the highest member of a series and from one of three foci, thumb and index, angle of mouth, or great toe.

ii *"March" of the convulsion* It usually starts in the highest members of the series and passes centripetally to the base of the limb. When the convulsion passes from the first

series, in which it has spread centripetally from the apex to a second or further series, it again begins in the lowest members of the new series.

iii *Attitude assumed by convulsed parts* Almost always the limb-series initially involved is flexor.

iv *Extent of the convulsion* Spasm may remain restricted to the muscles initially involved, or spread to and remain within the limb-series. In other cases all degrees of spread, until the convulsion becomes generalized, may occur.

v *Rapidity of spread* Convulsions that spread most rapidly spread farthest.

vi *Duration of fit* Fits which remain restricted to the small group of muscles in which they arise, tend to last longest and vice versa.

vii *The quality of the convulsion* Jacksonian convulsions are usually clonic, but may be tonic at first. Convulsions remaining narrowly localized tend to be clonic from the outset.

viii *Affection of consciousness* Convulsions restricted to a single series of the higher members of a series are not accompanied by alteration of consciousness. Consciousness is lost in spreading convulsions and at a stage varying directly with the rapidity of the spread.

ix *Influence of peripheral stimuli* Peripheral stimuli may increase, diminish or abolish the convulsions. These are exemplified by rubbing the part. This is true also of generalized fits. These stimuli are persistent and of some duration. Holmes (1927) has particularly drawn attention to the fact that local stimulation in the area affected by the Jacksonian attack may produce an attack.

x *Loss of power* Sudden loss of power may be a feature of some Jacksonian attacks or it may be the sole manifestation.

xi *Sensory concomitants* In some cases subjective sensory phenomena may precede or accompany spasms of loss of power appearing either in the weakened or convulsed or in some other part.

xii *Residual paresis of convulsed part* A transient paralysis of the muscles engaged in a Jacksonian convulsion may ensue.

Cortical representation of movements as exemplified by Jacksonian convulsions

Jackson repudiated the view that the march of a convulsion expresses a spread of excitation through the cortex from point to point, each point, as it is successively excited, discharging the movement it represents. Experiments already cited make it clear that the spread of the convulsions can occur even though the discharge remains restricted to the original cortical focus, which discharges successively its content of motor representations according to their threshold of excitability. A fit, beginning in one hand and then spreading in a hemiplegic fashion, has not the same pattern as one beginning in the hallux and affecting one half of the body. The total composition of the discharge may be the same, but its pattern or constitution is different. A spreading convulsion, therefore, does not necessarily imply a directly proportional spreading cortical excitation. The field of convulsion in the musculature is probably always much wider than the field of excitation in the cortex. A Jacksonian attack remaining localized is a relatively leisurely clonus of moderate intensity and often considerable duration. A compound order of spread, with increase in intensity and spread in incidence, is thus not readily applicable on the old punctate representation theory, but easily on Jackson's theory. The same applies to the fact that almost all Jacksonian attacks start from one of the three foci—thumb and index, angle of mouth, and great toe, and Walshe suggests that Jacksonian fits have their three characteristic foci of onset because the movements concerned are those which have the widest fields of low threshold excitability. It is generally assumed that, when a local cortical lesion provokes a convulsion, the focus of onset of the convulsion indicates that the lesion is in the corresponding cortical area. But this is untrue, as few lesions can be so small as to make so precise an exclusive localization possible, and it cannot be supposed that lesions in the cortex have some special affinity for the thumb-index, angle of mouth, or great toe areas. It is only to be explained on the mode of representation as suggested by Jackson.

The order of spread of a Jacksonian fit is not invariably that indicated by charts of the motor cortex. Thus, spread from upper limb to face should be, on this basis, from

shoulder to orbicularis, but it is usually from shoulder to angle of mouth. Such deviations from the pattern of the cortical chart are more easily accounted for on Jackson's hypothesis. Movements of both halves of the body are represented in each motor cortex, but not equally so. On Jackson's theory, a focal convulsion may become universalized from a single motor cortex. It follows that a destructive lesion in one hemisphere should produce more than hemiplegia. Gowers (1893) drew attention to the increase of tendon-reflexes invariably found on the side of the lesion in cases of hemiplegia, which is a further confirmation of Jackson's ideas. The loss of movements during and subsequent to Jacksonian attacks and the similar transient loss of speech, make it appear that such movements may be suddenly paralysed or put into spasm or both. It must be concluded that discharge from different cortical foci is involved—foci which inhibit movement in the first place and excite in the second.

[The paper summarized above is followed by 4 illustrative case-histories.]

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Intracranial Injuries

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THE NATURE OF CONCUSSION

by G. Jefferson, *British Medical Journal*, 1, 1-5, 1/1/44

In this address to the American Neurological Association, Professor Jefferson discusses the problem of unconsciousness produced by concussion, and gives the reasons for his belief that this is due less to disturbance of cortical function than to a focal disturbance at a lower level, probably in the brain stem.

During the last hundred years medical opinion has favoured first one and then the other of two chief hypotheses. On the one hand it was held that the nerve cells were paralysed by the vibratory effect of the force striking the head, *commotio cerebri*, and on the other hand that the disturbance of function was due primarily to impairment of the blood supply to the brain. This latter explanation has held the field for many years, especially since Trotter's opinion that concussion was due to the sudden cerebral anaemia produced by transient deformation of the skull.

Accurate post-mortem and experimental observations have been made by many authorities, but their interpretations have been at variance. Jefferson points out that the chief difficulties have been the inability to appreciate that commotion of the brain may disturb its action for much longer than a moment, according to the severity of the concussive force, that disturbance below cortical level could interfere with consciousness, and that an injury might paralyse nervous action without the necessity for its effects to be seen either macroscopically or microscopically. However, the experimental work on the transmission of impulses along axons and across synapses has proved that disturbance may easily occur without apparent alteration in structure.

The observations by Duret and others of coarse traumatic lesions around the fourth ventricle and in the medulla and

spinal cord focused attention upon the brain stem and lower levels, and further support was derived from the simple clinical observations of disturbance of pupil reaction, respiration- and pulse-rates, blood-pressure and such lower-level reflexes as the corneal and the pharyngeal. Denny-Brown and Ritchie Russell performed most noteworthy experiments on concussion, demonstrating that brain-stem paralysis undoubtedly occurs, that concussion is readily produced without skull-deformation, and that it is directly related to the acceleration imparted to the brain. Jefferson considers, therefore, that the prime cause of the phenomena of concussion is neuronal paralysis resulting from the direct effect of the force, and that alterations in cerebral blood supply are entirely secondary.

It is admitted that full consciousness, in the psychologist's sense, is mediated by the cortex, and that the post-concussive sequelae of focal paralysis and mental disorder, and necropsy findings, prove that cortical and subcortical lesions of varying degree occur, but the question must be answered: are these cortical lesions in the first instance the cause of stupor? Experimental and histological enquiry has been focused largely upon this question of the importance of the role of the cortex in traumatic stupor. Jefferson has long believed that the classical sequence of stupor—recovery—stupor due to intracranial bleeding provides the key to the problem.

There is experimental observation favouring the fourth ventricle and the mid-brain as the site of the lesion causing traumatic stupor and, in the human, injury at this level occurring as a result of certain neurosurgical operations provides valuable information. Thus, if death follows the extirpation of an acoustic neurofibroma there is nearly always unconsciousness from the time of operation. Unconsciousness can be readily produced by operative trauma in the posterior fossa, but ventricular drainage, although reducing the hemispherical pressure to zero, has no effect in restoring consciousness, although the cortical circulation and tissue-respiration must have been restored to normal. Pressure alone, of brief duration, will not of necessity abolish consciousness, but when it is maintained for some hours or days, as by a tumour or bleeding, the temporal lobe on each or both sides herniates into the tentorial hiatus. This herniation compresses the mid-brain and third-ventricle structures, and it is suggested that pressure at this particular site is the cause of stupor in such a case, and that it will persist until death, unless surgically relieved.

Three cases are quoted in order to support this view. In one, following an exploratory operation for an orbital tumour subsequently found to be an aneurysm, the patient never recovered consciousness and died 48 hours later, there having been considerable tachycardia and hyperthermia. Necropsy revealed a second aneurysm in the cerebellar vermis which had ruptured, and blood clot plugged the iter. That the patient died was not surprising, but the nature of the stupor was remarkable, in that occasionally she looked as though she might be about to wake up, half-opened the eyes, and appeared to be about to speak, but all efforts to make contact failed. The second case was one of pituitary adenoma, and again following operation there was a period of stupor before death, post-mortem examination revealed a clot in the third ventricle, some 3 cm in diameter. In the third case quoted, the patient died 18 hours after the partial removal of an acoustic neurofibroma, during this period she moved her arms freely, but her face was flushed and there was general vasomotor relaxation and free perspiration, without return of consciousness. At the necropsy, there were remnants of tumour extending into the tentorial hiatus, and discrete haemorrhages in the mid-brain, but the cerebral hemispheres were normal. From these and similar examples it is clear that intact vertical integrative pathways are of prime importance to consciousness, and that anatomically undamaged connections between the cerebral hemispheres are in themselves insufficient to maintain consciousness.

Jefferson feels that it would be helpful to define unconsciousness by some new term, instead of using a word which infers merely the reverse of a defined normal. He would like to speak in terms of unnatural or traumatic sleep, and suggests that 'parasomnia' would be a useful word denoting a state in which there are no verbal or mechanical responses to stimuli, except those of a reflex nature. Continuing this comparison with sleep, variations in the state of parasomnia may be looked upon as the arrest of moments of waking.

and the giving to them of duration. Restlessness and un-
ruliness indicate that cortical activities continue, and that
there is a high-level disturbance of its functions. On the
other hand, cortical lesions and massive excisions of the
cerebral hemispheres do not produce this state, although, as
has been shown, a small focus of injury in the posterior part
of the hypothalamus or in the mid-brain can do so. A
"waking centre" in some such region is therefore postulated
which, if damaged by trauma, results in hypersomnia. The
fact that it may not be possible to demonstrate such injury,
does not imply normal function. Although a mid-brain
lesion may thus have a profound effect, presumably by
interrupting integrative impulses in a caudal and rostral
direction, mental confusion, defective memory, and other
sequelae of concussion which may persist for long periods
may be explained by the disturbance of total brain function,
possibly due to cortical blocks. These conditions often
resemble the results of toxic agents, and it is not yet known
how long disturbance of neuronal function can continue
without there being demonstrable damage.

It is clear that our knowledge of the nature of the injury
is as yet very scanty. Valuable information has already
been obtained from electroencephalography, in which the
pattern after concussion may be similar to that seen in sleep.
Much has been made of oedema after brain injury, but
although there may be a slight increase in brain mass, oedema
of a severe grade is limited to the immediate periphery of
focal areas of contusion. It will be necessary to have more
detailed information of the result of trauma on the electrical
activities of cell-groups at different levels, and the changes
which may be induced in cell-respiration and in endocrine
requirements.

Jefferson finally enquires into the mechanism of death in
those cases which survive the immediate injury. So often,
the coarse findings at post mortem appear quite insufficient
to have been responsible for the final dissolution. Here
again he emphasizes the need for a re-orientation of ideas
with regard to the belief that abnormality of action must
always be accompanied by a gross (i.e. a demonstrable)
change. Why should an initial lesion severe enough to
cause neuronal paralysis be survived, and yet death ensue
some hours or days afterwards? It is presumed that injury
sets going a self-propagating process which, like disease,
leads sooner or later to death. Lesions of the vital centres
at the mid-brain level may conceivably give rise to a
progressive disturbance of various elements of the body
mechanism, which leads step by step, in a vicious circle,
to its dissolution.

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THE TREATMENT OF CEREBRAL CONTUSION

by L. Rogers, *British Medical Journal*, 1, 151-154, 6/2/43

The author, who is professor of surgery in the University of
Wales, points out that due consideration is not always given
to the complex pathological processes which result from
injury to the brain, and are involved in its recovery. Treat-
ment is often expectant when it should be more active. Con-
tusion produces brain swelling which, if retarded or prevented,
brings about compression of the cerebral vessels and im-
pairment of the cerebral blood supply. If this sequence of
events occurs, recovery of the bruised brain is incomplete
and is followed later by a varying degree of atrophy which
may be shown by air encephalography.

The object of treatment must therefore be to make pro-
vision for brain swelling, so that vascular compression does
not occur. This can be effected by the withdrawal of fluid
from the cerebro-spinal fluid spaces. The author recom-
mends that this should be done by continued gentle de-
hydration by retention enemas of 6 oz [about 170 cm³] of
30 % magnesium sulphate solution, given 6-hourly, by
nursing with the head raised and the neck free, by limiting
fluid intake to less than 1,000 cm³ daily, and by performing
occasional lumbar punctures.

This practice was begun in 1929 by the present author in
the Surgical Unit at the Royal Infirmary at Cardiff, and
550 cases have been so treated. There were 25 deaths and,
of the surviving cases, gratifying results were manifest by a
singular absence of sequelae. Restlessness is less pronounced
with this treatment, and if focal signs (e.g. a monoplegia or
a hemiplegia) arise these are found to be due to haemorrhage

(that is, to the accumulation of blood clot and not to cerebral
oedema). Focal signs in such circumstances therefore indi-
cate that craniotomy should be performed. Such signs are
only rarely encountered, but in the past, before the institution
of the dehydration treatment, these were seen more often as
they were sometimes the result of oedema. In those days
craniotomy was sometimes unnecessarily performed for
oedema which would have been prevented had dehydration
been instituted.

However, no two head injuries are exactly comparable, and
it is well known that remarkable and complete recoveries are
often made from extensive injuries to the skull and brain,
even with little or no treatment. It is difficult, therefore, to
assess the value of any particular type of treatment, but the
consistent absence of sequelae following the application of
such a treatment may be urged in its favour.

A quiet convalescence, and an absence of sequelae such as
the so-called post-concussional state, have been noticed after
the method of treatment advocated by the author. He
suggests that the post-concussional state may, in many cases
at least, be the result of failure to introduce effective treatment
in the early stages of cerebral contusion, and he believes that
resolution takes place readily and completely if the requisite
conditions for reparation are provided.

The essential principle of the method is the provision of
space to accommodate the brain-swelling and thus avoid the
consequent impairment of the cerebral blood supply.

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MECHANICS OF HEAD INJURIES

by A. H. S. Holbourn, *Lancet*, 2, 438-441, 9/10/43

The author of this paper is a physicist, who is one of a team
of workers investigating head injuries under the direction
of Professor (Brigadier) Hugh Cairns.

When the head receives a blow, the behaviour of the skull
and brain during and immediately after the blow is deter-
mined by the physical qualities of the cranium and its
contents and by Newton's laws of motion. The most
important of these qualities are

- a The comparatively uniform density of the intracranial constituents
- b The extreme incompressibility of the brain, for it does not appreciably change its size when subjected to a pressure which is uniform in all directions, the so-called hydrostatic pressure
- c It has a very small modulus of rigidity, i.e. the brain offers very little resistance to changes in shape compared with its resistance to changes in size
- d By contrast the rigidity of the skull is very great
- e The shape of the skull and of the brain are important in deciding the location of injuries
- f The brain is injured when its constituent particles are pulled so far apart that they do not join up again properly when the blow is over, and this pulling apart of the constituent particles is proportional to the shear-strain. The shear-strain present at any point in the brain should be at least a rough measure of the probability of injury at that point. Shear-strains are the cause of injury whereas compression- and rarefaction-strains are not. It has been found that nerves continue to conduct when subjected to a compression-strain due to pure hydrostatic pressure of 10,000 pounds per square inch [about 700 kg per cm²], a pressure vastly greater than anything which can arise in a head injury. If the pressure is not purely hydrostatic, i.e. if it is different in different directions, it must involve some shear, and very small pressure of this type is sufficient to injure a nerve.

The mathematical theory falls naturally into two halves
(i) Injury to the brain occurring as a result of distortion of the skull, (ii) injury to the brain occurring whether or not the skull is distorted.

Distortion of the skull is most severe near the point of impact and it consists mainly of an indentation of the skull. If fracture does not occur the shear-strains in the brain are mainly confined to a superficial region close to the dent, and the injury to the brain consists mainly of superficial bruising near the point of impact. Waves of compression and rarefaction (sound waves) emanate from this region and travel back and forth through the brain, but as only the

shears are injurious, these sound waves do not cause any damage. If the skull fractures, shear-strains are produced in the brain in the immediate neighbourhood, with again comparatively superficial injury of the brain-substance. At the line of fracture, haemorrhage may occur from a large vessel giving rise to an extradural, subdural or subarachnoid collection.

Other strains arise in the brain and would do so even if the skull were absolutely undeformable. These are called into play by the change in the velocity of the head caused by the blow. A linear acceleration imparted to the skull gives rise to no appreciable relative movement between the constituent parts of the brain, and the idea that the brain is loose inside the skull and that when the head is struck it rattles about like a dice in a box, thereby causing coup and contrecoup injuries is erroneous. The rotational acceleration forces are the main cause of brain injury. A simple demonstration of these forces is provided by a narrow necked flask filled with water and a few shreds of cotton wool. If the flask is suddenly rotated, the water tends to stay behind as indicated by the movements of the shreds of cotton wool. A particle of water attached to the inside surface of the flask becomes separated from a neighbouring particle not thus attached, and large shear-strains are produced. Water is of course less rigid than the brain, so that the effects of shearing-stress are exaggerated.

Models were made in order to study the situation of shear-strains as the result of rotational acceleration. These were the shape of cross-sections of the brain and made of 5% gelatin with $\frac{1}{2}$ % formalin added as a preservative. The gelatin was cast into a paraffin-wax "skull" and cut free with a taut wire, and the model was allowed to stand until slight adhesions grew across the water-filled gap between the "brain" and the "skull". The behaviour of these models when given a sudden rotation was studied in a circular polariscope. Though these experiments indicate the regions of brain liable to damage they give no information as to nature of this damage. It may consist of tearing of blood-vessels, tearing of axons, disrupting of cell-bodies, tearing apart of synapses, or injury of some parts of the nerve by amounts insufficient to cause actual breakage.

The diagrams given in this paper indicate the intensity and the distribution of shear-strains according to the plane in which the model is rotated. With a blow in the "occiput" causing rotation in the sagittal plane, great strain is produced at the tip of the "temporal lobe" and the under surface of the "frontal lobe" where the rotation of the "skull" is imparted to the "brain," and it is in these regions that considerable contusion is commonly found in post-mortem specimens. Over the vertex there is a fairly wide area where the brain tends to slip relative to the skull and much less strain occurs in this situation. In models it is not possible to reproduce the ventricles and other anatomical features, but in spite of these defects there is considerable correlation between experimental and post-mortem findings.

If there is no rotation, or only a very small degree, there can be no rotational injury, as happens if the head is fixed. Denny-Brown & Ritchie Russell (1941) found that it was difficult to produce concussion when the head was fixed, but easy when it was free to rotate. This is a further point suggesting that concussion is a rotational injury.

A rifle bullet has surprisingly small momentum and in consequence produces only a small degree of rotational velocity, and it is common experience that low-velocity bullets often do not produce concussion. But the visible injury to scalp, skull and brain in the path of the bullet, which depends mainly on its large kinetic energy, is very considerable. When the head hits a wall, the masses involved are large, and the kinetic energies are small, while the momenta are large, visible external injury is relatively small compared with the invisible damage due to rotation. Moving objects are usually less massive than the stationary objects against which one's head is likely to hit, and in consequence collisions with stationary objects usually produce more rotational damage than would be expected from the degree of external injury. This is probably the basis for the opinion of many that there is a difference whether the head, or the object causing the injury, is in motion. At certain points on the head, considerable force may be applied with practically no rotation and no ill-effect, as in heading a football. The opposite to this is exemplified by the ease

with which a boxer's knock out can be obtained by a force applied to the chin sideways and upwards.

For blows of long duration, shear-strains are proportional to the force, assuming that the direction and the point of application remain constant, i.e. the injury is independent of the time for which the force acts, and in this case the injury is proportional to the acceleration. Where the blow is of short duration, however, the injury is proportional to the force multiplied by the time for which it acts. That is to say, the injury is proportional to the change in velocity and not to the rate of change of velocity, and for this reason the term acceleration concussion may prove misleading. This change-over from one law of injury to another is still undergoing investigation.

Dr Holbourn also argues that on a mathematical basis there is no difference whether the rotation takes place about an axis through the centre of the brain or about a parallel one through a point in the neck. Also that in the case of rotations about any axis in the median plane, large-scale injury on one side of a symmetrical section of the plane is approximately the mirror image of a large scale injury on the other side. This is well shown in his models. In the brain, however, there are other modifying factors which must be considered and these give rise to minor details in the injuries which need not be mirror images. These mirror-image injuries are also confirmed by post-mortem findings.

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DEFECTS OF SMELL AFTER HEAD INJURY

by A. D. Leigh, *Lancet*, 1, 38-40, 9/1/43

A large series of cases of head injury has been carefully documented and followed up under the auspices of the Medical Research Council at a military hospital for head injuries. The author has extracted the clinical data referring to 72 of these cases (7.2% of the number under survey) who showed evidences of impairment of the sense of smell as a result of the head injury. Smell was simply tested by routine clinical methods, no special technique, such as that devised by Elsberg & Levy (1935), being used. All the cases except two had had a blunt injury. In 41 cases the anosmia was complete and in 31 it was partial, and there was parosmia (distortion of the sense of smell) in 12. In the 55 cases in whom the site could be determined, the injury was frontal in 30, occipital in 18, and parieto-temporal in the remaining 7. The injury was severe in most cases, the discharge rate from the service being higher in the group with defects of smell than in the total group of cases of head injury. In only 6 cases was there any recovery of the sense of smell. The onset of parosmia when it occurred was usually delayed, and it represented a stage of recovery in 3 of these 6 cases. Taste was disturbed in only 14 of the 72 cases, and in 9 of these primary tastes were preserved, while appreciation of flavours was lacking. The findings in this group of cases indicate that the connection between taste and smell is not so close as has been generally supposed. As 7 of the 14 cases with taste defects had a fracture running from the vault of the skull into the base, and as others had clinical signs of damage to the petrous bone, it is likely that quite a different mechanism was responsible for the defect in the sense of taste from that responsible for the loss of smell.

The findings reported in this paper show that anosmia occurs in severe cases of head injury and that the prognosis for recovery is very bad. Distortion of the sense of smell may be a stage in recovery, and the final result in parosmic cases may be favourable.

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HEAD INJURIES INVOLVING AIR SINUSES

by D. McKenzie, *British Medical Journal*, 1, 652-654, 13/5/44

The author of this paper, a Major in the New Zealand Medical Corps, writes as officer-in-charge of a base neuro-surgical unit in the Middle East. There is a serious risk of meningitis in patients with a fracture of the floor of the anterior fossa, by infection of the subarachnoid space from

one of the paranasal sinuses. The fracture may implicate the posterior wall of the frontal sinus, the cribriform plate, ethmoid cells, and the sphenoidal sinus, and the dura mater may be penetrated by a spicule of the fractured bone, but in this region it may be torn without actual penetration by bone. The bone is frequently very thin, and the dura mater firmly attached to it, so that distortion of the base of the skull at the time of the fracture readily splits the membrane. It is possible that infection may ascend into the subarachnoid spaces along a ruptured olfactory nerve in the absence of an actual tear of the dura mater.

The injury occurs as a result of a penetrating wound by a missile or from a blunt injury without an external wound. The author describes a series of 10 such cases, of which 4 were battle casualties and 6 due to blunt injury. Operation was undertaken in each without fatality. After describing the cases and giving details of the findings at operation, he discusses the diagnosis and treatment.

Cerebrospinal-fluid rhinorrhoea and *intracranial aerocele* are proofs that the dura mater has been torn and that meningitis is a real risk. In this series, aerocele did not develop, but rhinorrhoea occurred in 9 cases, either immediately after injury, or after several weeks. At times it may be difficult to ascertain the precise nature of fluid dripping from the nose, but if the flow is free, if it is accentuated by jugular compression, and if it contains sugar, then the diagnosis is certain. *Anosmia* may be due to local damage to the olfactory bulb but it may also be due to damage within the nose. The radiological recognition of the fracture is usually possible, though special projections may be necessary to demonstrate it, but extension of the fracture into the cribriform plate can usually only be surmised. An examination of the cerebrospinal fluid obtained by lumbar puncture is useful in the early diagnosis of meningeal infection, which may develop rapidly after the injury or may be very considerably delayed, and there may be recurrent attacks. Meningitis occurred in 2 of the 10 cases and was successfully controlled by sulphadiazine.

The author urges the operative treatment of these cases because of the potential danger of the condition, but operation should be postponed until the patient has adequately recovered from the injury to the brain. A preliminary prophylactic course of 6 g of sulphadiazine daily, continued for five days after operation, is recommended. Operation was performed under local anaesthesia and continuous intravenous pentothal, a bifrontal coronal skin-incision being utilized so that the scar was within the hair line. According to the extent of the lesion, a unilateral or bilateral frontal bone-flap was reflected laterally and the fractures were sought by stripping the dura mater. The tear in the membrane is more easily seen by this extradural approach, and the author prefers it to the intradural route. Small defects in the dura mater were sutured and larger ones were closed with a free graft of fascia lata, temporal fascia or muscle may be used for small defects. The need for most careful haemostasis is emphasized.

HEAD INJURIES IN CHILDREN AND THEIR AFTER-EFFECTS

by E. Guttman & H. Horder, *Archives of Disease in Childhood*, 18, 139-145, September 1943

Sixty cases of head injury in children are reported. Two-thirds of the cases were due to road-accidents. The incidence was higher in summer than in winter. Boys were more numerous than girls. The intelligence of the children was average and did not give any indication of their accident-liability. Fractures of the skull were more frequent than among adults. In the acute stage, emotional symptoms were more conspicuous than clouded consciousness and intellectual loss. The incidence of headache did not differ much from that in adults. Two-thirds of the cases were fit for discharge after 2 weeks' treatment in hospital. The absence from school due to the accidents was 2-7 weeks in half of the cases, less in one quarter of them, and more in the remaining quarter. The post-concussional syndrome was observed in 10% of the cases, its incidence depended to a large extent on environmental factors. Irritability was the most common after-effect. Persistent behaviour-disorder was rare in this series, as also was intellectual impairment.

VENTRICULAR CHANGES AFTER CLOSED HEAD INJURY

by H. Davies & M. A. Falconer, *Journal of Neurology and Psychiatry*, 6, 52-68, January-April 1943

This study was undertaken in an endeavour to assess in terms of present-day clinical knowledge the value of air encephalography in the investigation of cases of brain injury. In all the 100 patients it was considered that the symptoms did in fact result from head injury, and although cases of depressed fracture were included, those with penetrating injuries were not. No attempt was made to perform total air replacement, only sufficient air being introduced to obtain good ventricular filling. The amount of air introduced varied between 50 and 60 cm³, and in the majority of cases the cisternal route was used.

Standardized Lysholm projections were made so that comparable measurements of the ventricles were possible. The most reliable measurement of the lateral ventricles was found to be the diagonal diameter as seen in the brow-up projection, i.e. the distance from the inferomedial to the superolateral angle of the body, any inequality of the filling of the two ventricles being excluded by examination of the lateral projection in the brow-up position. Focal dilatation was determined by comparing the component parts of the lateral ventricles. Experiments to determine whether increase in intracranial pressure consequent upon the amount of air replacement might cause temporary ventricular distension, led the authors to the conclusion that this could be excluded. In a series of 50 cases used as controls the diagonal ventricular measurement lay between a minimum of 1.5 cm and a maximum of 2.2 cm. As this measurement exceeded 2 cm in only 2 cases, it was felt that an arbitrary upper limit of normality might be fixed at 2 cm. In no control case was there a difference of more than 0.2 cm between the measurements of the two lateral ventricles. Measurements of the width of the third ventricle were made, but it was felt that the normal range of variation was too wide to afford any significant information.

In accordance with these standards of normality, the ventricles were enlarged in 69 of the 100 cases of closed head-injury. In some the enlargement involved only a part of the lateral ventricle (focal dilatation) and in others the whole of the lateral ventricle was affected (generalized dilatation), and the cases could accordingly be arranged in four groups:

- i Without dilatation of the ventricles, i.e. normal encephalogram 31 cases
- ii Focal dilatation 15 cases
- iii Generalized dilatation, (a) one ventricle only 21 cases, (b) both ventricles 26 cases
- iv Focal dilatation superimposed on general dilatation 7 cases

Although ventricular dilatation occurred in a high proportion of these cases, the series was highly selected in that, with one exception, all the patients showed either some residual complication due to the head injury or else some unusual feature during the acute stage, viz. prolonged post-traumatic confusion, or epilepsy. An attempt was made to correlate the type and extent of the ventricular dilatation with the severity of the head injury, with the site of injury, and with the time after injury when the dilatation became apparent. The criterion adopted for assessing the severity of head injury was the duration of post-traumatic amnesia. In the table analysing these results, the frequency of ventricular dilatation is shown to rise steadily with the increasing duration of the post-traumatic amnesia, from 33% in cases where there was no post-traumatic amnesia to 92% in cases where the post-traumatic amnesia lasted for longer than a month. The degree of ventricular dilatation increased with the duration of the post-traumatic amnesia, out of 18 cases in which post-traumatic amnesia was less than one day, 2 cases (11%) had focal dilatation and 3 cases (17%) had generalized bilateral dilatation. Out of 13 cases in which the post-traumatic amnesia exceeded a month, 2 cases (15%) had focal dilatation, and 7 cases (54%) had generalized bilateral dilatation. From the relatively few cases in which there was a record of the cerebrospinal-fluid examination during the first week after injury it appeared that the presence of blood in the fluid, an indication of a severe degree of cerebral trauma, was associated with a subsequent dilatation of the ventricles.

Excluding cases with a fracture of the skull, there appeared to be no correlation between the site of the dilatation and the site at which the violence had been applied. Dilatation of the ventricles was more frequently observed in cases with a fracture of the skull than in those in which no fracture occurred. In those cases of fractured skull in which focal dilatation was detected it was found that the ventricular enlargement commonly occurred immediately beneath the site of fracture (9 out of 11 cases). It was concluded that dilatation commenced in less than three weeks and reached its maximum within four weeks.

Correlation between the degree and type of the ventricular enlargement, and the clinical features of the case was not always obvious. In one case generalized bilateral ventricular dilatation of considerable degree might be associated with marked residual neurological signs and in another case with none at all. One ventricle might be dilated more than its fellow, but the neurological signs present were referable to the side with the smaller or more normal ventricle. Frequently the enlargement of the ventricles could be correlated with residual neurological signs such as hemiparesis, aphasia, etc., and about 89% of cases with persistent focal signs showed ventricular enlargements. In cases of head injury without persistent signs of focal cerebral damage the ventricles were dilated in only 62%. A further analysis was made in order to relate the dilatation with the typical features.

Head injury without unconsciousness There were 6 cases in this group, 4 showed normal ventricular outline and 2 dilatation. All the cases were investigated on account of persistent features considered to be due to the injury, such as post-traumatic syndrome, post-traumatic epilepsy, and residual pyramidal signs.

Head injury without residual sequelae Of 9 such cases, in only 1 was the ventricular system normal, this was an example of comparatively mild straightforward head injury, and encephalography was undertaken because of a single convulsive attack occurring one hour after the injury. In 1 case there was symptomless focal dilatation beneath a healed compound depressed fracture, and the other 7 cases were examples of Korsakow's psychosis which eventually made complete recovery. This important group demonstrates that post-traumatic ventricular dilatation, even of moderate degree, is not necessarily associated with permanent psychological or neurological disturbance.

Head injury with residual neurological signs (i) Residual pyramidal signs. There were 24 cases in this group and all except two showed dilatation of the ventricles. In 6 there was focal dilatation, in 6 bilateral dilatation, in 3 focal and unilateral dilatation, and in 7 unilateral dilatation. In all except 1, the bigger ventricle was on the side opposite to the residual pyramidal signs, in 1 case this relationship was further emphasized in that there were bilateral pyramidal signs, and bilateral ventricular dilatation, and the side of greater ventricular dilatation was opposite that of the greater motor signs. In the one exception to this association, a pronounced residual left hemiparesis was observed in association with marked focal dilatation of the anterior part of the left lateral ventricle. (ii) Hypothalamic and/or brain-stem signs. There were 4 in this sub-group and only one showed ventricular dilatation, none had a fracture of the skull visible in the x-ray films. In 3 of the cases there was prolonged post-traumatic amnesia, residual cerebellar ataxia on one side but no motor weakness, and associated in 1 case with nystagmus and dysarthria. In 1 case during the acute stage following the injury there were the postures of decerebrate rigidity with righting reflexes. This patient had a residual dementia, weakness of one arm and spasticity of both lower limbs. (iii) Residual optic radiation defect. In 3 such cases there was a fracture in the parieto-occipital region suggesting localized injury of the posterior part of the cerebral hemisphere, and in no case did dilatation of the related part of the lateral ventricle occur. In one case the size of the ventricle was normal, in another there was contralateral dilatation, and in the third generalized symmetrical dilatation. (iv) Cranial nerve palsy. The cases included in this group only those in which the nerves were damaged presumably within the cranial cavity, but not in their course through the skull. There were 16, 12 showing anosmia, 4 chiasmal lesions, and 3 oculomotor nerve palsies, but in only 5 cases were these palsies the only residual neuro-

logical sequelae. The ventricles were normal in 3 of these. It was thought probable there was no direct relationship between size of the ventricles and cranial nerve palsy.

Post-traumatic syndrome and post-traumatic intellectual deterioration Twenty-nine cases were classified as examples of post-traumatic syndrome and the injuries as a whole seemed clinically less severe than those in the second group. Nearly half had ventricles of normal size and shape, and amongst the others were examples of all types of dilatation. There were 24 cases of post-traumatic intellectual deterioration, and in these only 3 had ventricles of normal size. All varieties of dilatation were detected, but generalized bilateral enlargement preponderated.

Post-traumatic epilepsy Cases with antecedent attacks or with a known family history were excluded, also those in which the convulsive disturbance occurred during the acute stage of the injury. There were 19 cases in all, and there appeared to be no relation between the incidence of epilepsy and the severity of the injury as measured by the duration of the post-traumatic amnesia or by the degree of ventricular dilatation.

Discussion Summarizing their findings, the authors conclude that ventricular dilatation of either a focal or a generalized character often follows a closed head injury, and although it may occur after apparently mild injury the frequency with which it is found increases with the severity of the trauma. Appearing within two or three weeks of the injury, the enlargement may reach its maximum within a month. It does not appear to be influenced so much by the site of impact as by the presence of a fracture of the skull, and in particular, focal dilatation may develop beneath such a fracture. There is usually an obvious relationship between the clinical signs and the encephalographic appearances, and cases with residual pyramidal signs are frequently found to have a ventricle dilated on the appropriate side. The ventricles are usually dilated in cases with marked intellectual and mental deterioration, but they are usually normal where the disorders are of a subjective character. Post-traumatic epilepsy does not appear to be connected with changes in the ventricular outline.

The findings in this series do not support the views of other writers that air encephalography can be used as a certain means of differentiating between cases with genuine disabilities, and those with functional disturbances. A normal encephalogram in a given case does not prove that the symptoms are functional, because permanent organic damage can occur without resulting in ventricular enlargement. The distribution of air in the subarachnoid spaces over the cortex was not studied, because the authors chose the method of cisternal introduction of air as causing less disturbance to the patient, this method does not usually give a clear demonstration of subarachnoid spaces, but it is considered to give better pictures of the ventricles, with smaller quantities of air.

Ventricular dilatation after recovery from a head injury indicates an atrophic process in the brain, this may be due to obstruction of the cerebrospinal fluid pathways, or the result of pathological changes produced in the brain substance itself by the trauma. The two types of dilatation, focal and generalized, are probably produced by different mechanisms. Focal dilatation probably results from the resolution of local pathological changes in the brain tissue occasioned directly by the injury, the frequency with which it occurs beneath a fracture of the skull supports this view. Other factors affecting the brain more widely must operate in cases of generalized dilatation. These factors include brain oedema, dilatation of cerebral capillaries and veins, endarteritis and traumatic subarachnoid haemorrhage. It is difficult to explain, however, why such dilatation may be restricted to one ventricle, though this may be the result of a vascular disturbance.

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SOME OBSERVATIONS ON THE CEREBROSPINAL FLUID IN CLOSED HEAD INJURIES

by J. H. Paterson, *Journal of Neurology and Psychiatry*, 6, 87-91, July-October 1943.

These observations are based upon a series of 300 cases of acute closed head injuries, excluding such in which the verified complications of extradural and subdural haematoma

and meningitis occurred. The cerebrospinal-fluid pressure at the initial lumbar puncture during the first week after injury was above the normal (180 mm) in 85 of 235 cases (i.e. 36%), and in only 11 was it above 300 mm. When the pressure-readings were related to the duration of post-traumatic amnesia (chosen as the criterion of severity of brain injury), there was a significant increase in the proportion of cases of raised cerebrospinal-fluid pressure in the more severe injuries. Nevertheless, in 24 cases with post-traumatic amnesia of over 7 days, the initial pressure was not raised in 29%. The cerebrospinal-fluid pressure in cases where initial lumbar puncture was not performed until the second or third week after injury is compared with those in which it was performed within the first week, all cases being grouped according to the length of post-traumatic amnesia—under 24 hours, 1–7 days, over 7 days. It was found that, notwithstanding the duration of post-traumatic amnesia, initial pressures in the second and third week were within normal limits. The author concludes that there is a natural return to normal cerebrospinal-fluid pressure within the week after injury, without resort to further lumbar puncture.

Blood in the cerebrospinal fluid in significant amounts was found in 120 cases, and it usually cleared naturally by the end of the first week. The author doubts whether repeated puncture hastens this natural rate of clearance. Further delayed subarachnoid haemorrhages may occur, sometimes with clinical manifestations, where repeated punctures had been performed there were in 16 of 42 cases late increases in the cerebrospinal-fluid erythrocyte-count. This usually occurs during the first week. Increase in the erythrocyte count without clinical manifestations may not be due to fresh bleeding, but possibly to variation in the freedom of circulation of the cerebrospinal fluid, or to loculation. It is shown that, when the post-traumatic amnesia is over 24 hours, subarachnoid bleeding is the rule, but there is little correlation between the amount of bleeding and the elevation of cerebrospinal-fluid pressure, unless haemorrhage is considerable.

Drowsiness or stupor was found to be more common amongst the patients with a raised cerebrospinal-fluid pressure. Thus, the proportion of alert to drowsy patients in which the pressure was 250 mm and over was roughly 1 to 3, but the comparable ratio in patients with normal pressure was roughly 3½ to 1. Similarly it was shown that if the cases were grouped according to the increasing degree of subarachnoid bleeding, the proportion showing drowsiness likewise increased.

The author emphasizes the frequency of a normal or only slightly raised pressure, which is of interest in view of methods of dehydration which are in vogue. He doubts whether a raised pressure by itself plays an important role in the production of symptoms and signs in acute head injuries. He discusses the theories advanced to explain raised pressure in uncomplicated cases, and concludes that this problem remains unsolved. Blood in the cerebrospinal fluid may arise from a ruptured venous sinus, and there may be little damage to brain itself by the injury. This explains the rare cases of heavily bloodstained cerebrospinal fluid with relatively little clinical evidence of brain damage. But most commonly the bleeding results from cortical laceration, and therefore the severity of bleeding usually runs parallel with the damage to neural tissue. This does not conflict with Jefferson's views that traumatic stupor is due to interference with brain-stem function.

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THE EFFERENT PATHWAY FOR PUPILLARY CONTRACTION

by P W Nathan & J W A Turner, *Brain*, 65, 343–351, December 1942

Working at a military hospital in Britain devoted to head injuries, the authors present strong clinical evidence that there must be two separate pathways for the pupillo-constrictor fibres in their course from the third nerve nuclei to the eye. It has in the past been generally agreed that these fibres run from the nucleus with the nerve to the inferior oblique muscle, branch off to a cell station in the ciliary ganglion, and so form the short ciliary nerves which end in the ciliary plexus. The authors argue that if this is the only pathway used, its complete section would cause the pupil to be fixed to light and to accommodation. They

then produce evidence showing that a pupil fixed to light yet reacting to accommodation may be produced by a lesion outside the brain stem. Foerster, Gagel & Mahoney (1936) showed that such a pupil (the Argyll Robertson pupil) can be produced in some apes by removal of the ciliary ganglion, and thought that there must be a separate constrictor nerve for light and accommodation.

The present authors describe the findings in two soldiers who had an Argyll Robertson pupil on one side as the result of a peripheral lesion. In one case it was due to a piece of shrapnel and in the other to a fracture of the greater wing of the sphenoid. The authors summarize the findings in eight previously recorded similar cases which all fulfil the criteria needed to show that the lesion is in the efferent pathway, while the afferent is intact, namely, (a) the normal pupil contracts on illuminating the abnormal eye, (b) the abnormal pupil does not contract to direct or consensual light, (c) both pupils constrict normally on convergence and accommodation and dilate again afterwards, (d) the lesion is peripheral.

An Argyll Robertson pupil of this sort may be due either to the passage of the stronger nervous impulses only, assumed to be due to light, over a single damaged pathway, or to destruction of one of two pathways serving light and accommodation separately. If the first possibility were the case, all recovering cases of third nerve palsy would show an Argyll Robertson pupil, but this is not found to be so. Consequently the authors searched for a second pathway for the pupillo-constrictor fibres to convergence, and they explored five possible known routes—(i) the sympathetic, (ii) the nerves in the external ocular muscles, (iii) the optic nerve, (iv) the nasociliary nerve, (v) the long ciliary nerve. They exclude all these possibilities and conclude that the pathway may be through the fine myelinated nerves which go to the episcleral ciliary ganglia described by Axenfeld in 1907. As Givner (1939) has recently shown, these episcleral ganglia occur normally in man, and as the parasympathetic system usually has a ganglion cell near the organ innervated, it may well be that constriction of the pupil in response to accommodation and convergence is brought about by these minute episcleral ganglia, which have hitherto been considered mere anatomical curiosities with no known function.

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INDIRECT INJURIES OF THE OPTIC NERVE

by J W A Turner, *Brain*, 66, 140–151, June 1943

This paper deals with damage to the optic nerve as a result of a head injury in a manner other than direct involvement by a projectile. It is based on 46 cases and includes 25 drawn from a consecutive series of 1,550 head injuries admitted either to an Emergency Medical Service hospital or to a military hospital for head injuries. The author, who was a medical officer at each of these hospitals in turn, is now neurologist to one of the Home Commands of the British Army.

The rate of incidence of damage to the optic nerve is assessed as 1.5% of head injuries, whereas Rowbotham (1942) gives a figure of only 0.5%. The latter, however, appears to include only complete injuries of the nerve, whereas the present author includes partial injuries. An analysis of the comparative incidence of damage to cranial nerves, drawn from the same series of 1,550 cases gives the following table.

Olfactory	119
Optic	25
Optic chiasm	3
Oculomotor	15
Trochlear	15
Trigeminal or its major branches (excluding supra- and infraorbital involvement)	3
Abducens	15
Facial	46
Vagus	1

It is noticeable that the optic nerve is more frequently damaged than any individual nerve of the oculomotor group.

Motor-cycle and cycle accidents accounted for more than half of the 46 cases of optic-nerve damage. In 35, the point of impact was judged to be on the forehead or supra-orbital region (only one of these being contralateral), and in 6 others in the region of the external angular process. In 4 cases the point of impact was not determined but in 2 of these it was probably frontal. In only one was there evidence of a posterior injury—an open fissured fracture in the parietal region from air-raid debris.

There did not appear to be any close correlation between the severity of the head injury (as judged by the length of post-traumatic amnesia) and the incidence or severity of optic nerve damage, though the majority of cases were associated with severe concussion. In all cases in this series the effect was immediate and no examples of delayed blindness were observed. If useful vision is going to be recovered, improvement starts about the third or fourth day and progresses rapidly. It is probable that full recovery never occurs, and the permanent effects included 13 cases with no perception of light, 8 cases with scotomata, and 19 cases with defects predominantly in the peripheral visual field. There are no visible ophthalmoscopic changes in the early stages, and none may ever be seen in cases of partial injury. Even in complete injuries, pallor of the optic disc is not usually noticeable until 3 weeks have elapsed, it may be later in cases of partial damage.

Unless there is concomitant damage to the 3rd cranial nerve, the pupil is not altered in size and may retain the normal light-reflexes if the degree of damage to the optic nerve is slight. This statement contradicts the assertion by Ternin (1935) that immobility of the pupil to light is a constant accompaniment of an optic nerve lesion. Concomitant damage to other cranial nerves was frequently found, especially the olfactory and the oculomotor, but only one patient had a complete sphenoidal-fissure syndrome.

Radiologically it is rare for there to be any demonstrable damage to the region of the optic foramen, even when special views are used for its demonstration and comparison with the opposite side. Thirty-seven had these special views but in only 4 was any abnormality visible. Possibly more might be seen if tomography were used.

The author draws attention to the fact that fissured fractures claimed by other authors (Barkan & Barkan, 1928; Rollet, Paufigue & Levy, 1930) to be responsible for damage to the optic nerve, cannot be more than an accompaniment of the nerve damage. In rare instances the nerve may be compressed by a fractured anterior clinoid process. A number of authors accept the view of Pringle (1922) that damage to the nerve is caused by compression due to haemorrhage beneath the sheath. Turner believes that a vascular lesion (either haemorrhage or thrombosis) of the septal arteries or of the recurrent branch of the retinal artery within the substance of the nerve as it lies in the optic canal is a more satisfactory explanation. He is not able to adduce pathological evidence as none of his cases has died.

In conclusion, attention is drawn to partial injuries of the nerve, where visual acuity may be almost normal but scotomata may be present. In only 4 cases out of 37 specially investigated was there any demonstrable radiological abnormality of the optic foramen, and it is suggested that the mechanism of injury is intracranial vascular damage.

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FACIAL PALSY IN CLOSED HEAD INJURIES THE PROGNOSIS

by J W A Turner, *Lancet*, 1, 756-757, 10/6/44

A series of 70 consecutive cases of traumatic facial nerve palsy in closed head-injuries has been studied from the point of view of prognosis. The author, who is neurologist to one of the Home Commands of the British Army refers to his analysis of 1,550 consecutive cases of head injury (Turner, 1943) in which, of all the cranial nerves, the facial

suffered injury only less frequently than the olfactory. The injury tends to be associated with a severe degree of concussion, though not necessarily so. There is no constant position of impact to the head.

Traumatic facial palsies are of two types—those occurring at the time of injury, and those delayed in onset. The latter may occur at any time between the 2nd and the 8th day. In this series there were 36 immediate palsies and 34 delayed. Of the delayed palsies 11 were complete and 22 partial, while one was bilateral with both sides probably partial, though not observed by the author at the time of onset. In 19 cases recovery started within a few days of onset and progressed to complete recovery in less than 3 weeks. All the others, except 2, also recovered satisfactorily within 4 months. Of the two unsatisfactory cases, one developed acute otitis media on the 5th day, simultaneously with the facial palsy, which remained complete 6 months later, the other showed incomplete recovery with "associated" facial movements 8 months later.

"Associated" facial movements (for example, eyebrow and lip moving together when only one movement was intended) occurred more frequently in the cases of recovery after immediate facial palsy, and this group showed a considerably higher proportion of slow and incomplete recoveries. Of the 36 in this group, 17 were partial and 19 complete, 9 began to recover in a few days and were normal in 3 weeks, 15 began to recover in 3 weeks and were normal in 6-8 weeks, 3 began in 6-8 weeks and were normal in 3 months, 6 began after 3 months and were never normal, while 3 remained complete for 2 years or more. Of the last 3, 2 had been complicated by acute otitis media.

The aetiology is assumed to be a laceration of the nerve or an intraneural vascular accident in the case of immediate lesions, while pressure of blood on the nerve in the aqueduct of Fallopius is likely to be present in the delayed cases. Both types are probably always associated with fracture of the petrous temporal bone, though this is rarely demonstrable by radiography. The 8th nerve is commonly involved but not necessarily so, and the presence or absence of this complication is of no prognostic value.

The treatment recommended is expectant, with facial splintage, electrical stimulation, and facial exercises in the more slowly-recovering cases. The present series of cases argues against any operative intervention until at least 6 months have elapsed, and even then electromyographic records should first be made to determine whether any motor units are reaching the muscles (Weddell, Feinstein & Pattle, 1943).

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PROLONGED POST-TRAUMATIC AMNESIA FINDINGS AT OPERATION

by A A McConnell, *Lancet*, 1, 273-274, 28/2/44

The author, who is the senior surgeon of the Richmond Hospital, Dublin, describes 6 cases in which post-traumatic amnesia continued for longer than 6 days. The first was seen in 1930 and an exploratory burr hole, made because a fracture could be seen crossing meningeal vascular markings, revealed a collection of clear fluid between the arachnoid and the dura. The significance of the finding was not appreciated at the time, but during the past 3 years 5 cases of prolonged amnesia have been seen in a series of 53 closed head-injuries. All 5 of these have been explored by a single burr hole 1 cm in diameter made on each side of the skull. In all but one, a definite collection of fluid was found beneath the dura and the brain remained 1-2 cm distant from that membrane. The interval between injury and operation varied in these cases between 6 and 21 days. The fluid was definitely pathological, with a protein content varying between 1.8 and 3.5 g. per 100 cm³. It was often found on both sides, varying in volume between a few cm³ and more than 200 cm³.

The term suggested for the condition is subdural effusion though other authors have suggested subdural fluid accumulations, "subdural hygroma" or subdural

hydroma" The fluid is usually considered to be cerebrospinal fluid which has escaped through a small tear in the arachnoid, but it becomes independent of the cerebrospinal circulation and is not removable by lumbar puncture

Contrary to the general opinion that the symptoms and signs of subdural effusions are similar to those of subdural haematoma, the author stresses the fact that a subdural effusion may be present without producing any of the symptoms or signs which suggest haemorrhage. He advocates the performance of operation in the great majority of cases of prolonged post-traumatic amnesia, and points out that the condition cannot be diagnosed nor can the fluid be removed except by opening the skull

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TRAUMATIC DILATATION OF THE CEREBRAL VENTRICLES

by D W C Northfield, *Journal of Neurology, Neurosurgery and Psychiatry*, 7, 1-6, January-April 1944

Cases of traumatic dilatation of the ventricles may be separated into three groups, but any one case may belong to more than one group

i Local bulging of the ventricles, which in extreme degrees presents the appearance of a diverticulum. This condition is not discussed, as the atrophy of the brain and the formation of a cerebral or a meningocerebral cicatrix have factual proof

ii The enlargement involves the whole of one lateral ventricle, either on the side of the head which received the blow or on the opposite side. It is tempting to assume that an oedema of one hemisphere might lead to such dilatation, but oedema of this extent has not yet been satisfactorily proved. Contralateral enlargement seems related to contrecoup effects, but that does not explain the precise mechanism of the dilatation. Raised intracranial pressure by itself cannot be the cause, unless a softened state of one hemisphere allows its ventricle to dilate

iii General symmetrical enlargement of the lateral ventricles, rarely involving the third and fourth ventricles

The adoption of a normal size of ventricle is difficult because the various methods of measuring the ventricles do not take into account the variations in size according to age, and do not give due weight to the lesser degrees of enlargement, in which there may be only slight increase of the lateral diameter but considerable rounding of the angles, and deepening of the body. The incidence of traumatic ventricular dilatation is unknown and can be obtained only when every case of head injury is investigated by this method. Such a thorough investigation is not likely to be accepted. Even clinically mild injuries may cause slight dilatation, but the figures available relate only to selected cases. Bielschowsky (1928) described a series of 106 cases investigated at periods after the accident of from several months to years. All these cases were selected by reason of abnormalities of the cerebrospinal-fluid (CSF) system which were present in varying degrees in all. Of 48 cases of the so-called post-contusion syndrome with no focal signs of cerebral damage, 77% showed abnormal encephalograms comprising for the most part various degrees of dilatation. In 38 cases in which focal signs were also present (in these the injury was probably more severe) there were 87% of abnormal encephalograms, and in a third group of 30 cases of traumatic epilepsy, there were also 87%

The author makes no attempt to gauge the frequency of ventricular dilatation and admits that the utilization of encephalography has been somewhat haphazard, but several cases are quoted to illustrate certain points. In the first case the clinical findings pointed unmistakably to a mid-brain contusion, and at operation there was good evidence of a right hemisphere contusion. Encephalography demonstrated considerable cerebral atrophy, especially of both frontal lobes. Eventually no impairment of intellectual capacity remained, and the patient returned to the service as an electrical engineer. The blow struck the back of his head, and radiographically there was evidence of bifrontal atrophy, but no unequivocal clinical evidence to confirm this, and there was no anosmia. The second patient was under observation for 18 months following a head injury associated with considerable mental confusion, which was followed by a small chronic subdural haematoma which was evacuated. Encephalography performed on several

occasions during this long period demonstrated a steady enlargement of the ventricles, and line drawings are given to demonstrate this progressive enlargement. The third case quoted is somewhat similar, and encephalograms performed after an 18-months' interval again showed ventricular enlargement over a long period of time. The fourth case is quoted to demonstrate the difficulty of deciding whether the ventricles are of normal size or not. As judged by measurement, the size would be passed as normal, yet to an accustomed observer, the appearance is one of slight dilatation

In the argument which follows, the author discusses the possible causes of ventricular dilatation in the light of present day knowledge. Common experience shows that the degree of ventricular dilatation is usually greatest in those patients who have sustained severe injuries, as judged by such criteria as prolonged unconsciousness, presence of focal signs of cerebral damage, temporary traumatic dementia and the presence of blood in the CSF. Prolonged disturbance of consciousness and of mental function may mean a widespread or diffuse disturbance of neuronal function, and Denny-Brown & Russell (1941) in their experiments on concussion drew attention to the widespread nature of neuronal paralysis, and its longer duration when the force producing it was increased. Thus it is possible that the process leading to dilatation of the ventricles may be due to a generalized effect on the brain although its microscopic pathology has not yet been identified

Broadly speaking, the ventricles may dilate as a result of a disturbance of the cerebrospinal-fluid system, or they may dilate as a result of some change taking place primarily in the brain tissue, i.e. hydrocephalus *ex vacuo*, it is possible that both of these processes may be operative in any given case. Disturbance of the CSF-system may arise from excessive production, delayed circulation, or impaired absorption of the fluid. Excessive production can be significant only if the production-rate is greater than the absorption-rate, and from the evidence available this seems highly improbable, provided the absorptive mechanism is undamaged. There are no observations in the human as to the rate of secretion after head injury, or even in the normal. Experiments in animals suggest that following a blow of the skull, there may be an excessive secretion of fluid from the choroid plexus, and Rand & Courville (1931) noted histological changes in the choroid plexus which they ascribed to an excess of fluid being passed into the ventricles. Thus there is some suggestive evidence of increased production of CSF following a head injury, and the problem merits further investigation

Delay in the circulation and in the absorption of the fluid have been investigated more freely, both experimentally and by the histological changes seen in cases of injury, and in cases of hydrocephalus secondary to birth-injury. These findings suggest that occlusion of the leptomeningeal spaces may occur as the result of extravasation of blood, but it is not known whether the obstruction is permanent, or whether fresh leptomeningeal spaces may subsequently be opened up comparable with the canalization of a venous thrombosis. Furthermore, if such an obstructive element were active, then the CSF-pressure should be persistently raised, but in cases of head injury in which the pressure is raised, it remains so for only a few days after injury, and it is not known whether the ventricles remain permanently dilated after a transient intracranial hypertension. Bielschowsky made some investigations into this possible delay of fluid circulation, stating that in 54% of his cases the pressure was over 200 mm, but such a finding is not in accordance with common experience. Tests of the rate of absorption of the CSF were made by the iodide method of Forster, and there was marked delay in 58%. Encephalography does not help here, because often the cortical spaces fill with air, so that occlusion cannot have occurred. If there is impairment of the absorptive powers of the arachnoid villi, then dilatation of the cortical spaces may occur. In Bielschowsky's series there were 28 cases of extensive collections of cortical air and in 17 of these there was delayed absorption according to the iodide test. Thus, although there is some evidence that disturbance of the CSF-system may lead to traumatic ventricular dilatation, the clinical and histological observations need further confirmation, and data of the rate of secretion, and absorption of CSF in normal and in traumatized subjects must first be obtained

Discussing changes occurring primarily in the brain tissue the author comments that there is even less reliable information, although the view favoured by most writers is that generalized oedema of the brain leads to gliosis and atrophy, there are very few facts to support it. To substantiate this claim extensive serial sections on the whole cerebrum would need to be examined, and there would have to be a great number of widespread samplings of brain to estimate water content. The area of the brain available to inspection through a burr hole, which is the common form of exploratory operation in acute head trauma, is inadequate for the surgeon to pass any comment on the state of the brain, apart from such obvious local changes as contusion. The fact of generalized brain oedema has therefore yet to be proven. Other observations, both experimental and from histological examination of human material, afford another possible explanation for traumatic ventricular dilatation. The hypothesis is that there may be an outpouring of CSF from the choroid plexus causing a transient dilatation of the ventricles, and that if the ependyma is in a damaged condition, as appears possible, the fluid by seepage into the brain substance might give rise to oedema. In this connection it is noteworthy that Greenfield (1942) has described histological changes around the wall of the ventricle in cases of rapid hydrocephalus which he attributes to such a seepage of the fluid through the ependyma into the brain.

Summarizing, it is clear that the cause of traumatic ventricular dilatation remains unidentified. In order to solve this problem certain facts are needed: (i) the normal size of the ventricles, the variations with age and the incidence of traumatic dilatation, (ii) the rate of secretion and of absorption of CSF in health and after head injury, (iii) whether blood in the CSF leads to permanent impairment of its channels and its absorptive organs, (iv) the occurrence or otherwise of generalized brain oedema, (v) the histological picture of traumatic dilatation.

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NOTE ON A COMMONLY UNRECOGNISED TYPE OF INJURY TO THE CERVICAL SPINE AND SPINAL CORD IN ASSOCIATION WITH HEAD INJURIES

by F. M. R. Walshe, *Lancet*, 2, 173-175, 5/8/44

Setting aside the well-known complications of frank fractures and fracture-dislocations of the cervical spine (especially between C.5 and C.6) associated with head injuries (Jefferson, 1928), the author, who is physician to the National Hospital, Queen Square, draws attention once more to a condition which he has reported previously in association with Ross (Walshe & Ross, 1936).

The cases with which he is concerned are those in which the spinal-cord symptoms are easily overlooked at the time of the head injury. The latter is often somewhat trivial—sometimes without even transient unconsciousness—but both the patient and his doctor are liable to ascribe any unusual symptoms to the cerebral damage or to neurosis.

Characteristically, if the patient does not lose consciousness, he describes a tingling or "dead feeling" from neck to feet at the moment of injury. Sometimes there is inability to move the limbs for a few minutes. The tingling in the limb may persist and be increased by activity and by certain movements of the head and neck, especially full forward flexion. The patient is often able to return to work but finds his arms clumsy and somewhat weak. After a very few weeks he notices that there is some muscle-wasting, sometimes confined to the small muscles of the hand but sometimes also in the upper arm and shoulder girdle. Muscular fibrillation may be present, but is not so constant nor so widespread as in progressive muscular atrophy. The muscles are usually tender to pressure. On examination at this stage no objective sensory loss can be demonstrated, though the paraesthesiae (and sometimes radiating pain) persist for weeks or months.

The state of the tendon reflexes in the arms is of the greatest diagnostic importance. The triceps reflex is commonly

increased, the biceps reflex normal, diminished or absent and the supinator reflex normal, diminished or absent, but its elicitation usually produces brisk flexion of the four fingers. This unequal affection of the arm reflexes indicates a focal cervical cord lesion and differentiates the cases from amyotrophic lateral sclerosis. The only other finding in the neurological examination is usually some evidence of slighter or greater involvement of the pyramidal tracts to the trunk and legs. Normal sphincter action is the rule from the outset.

The course of the case varies: some make a steady recovery to normality or near-normality, others remain with a fixed degree of disability, and others deteriorate during the period of muscle- and joint changes.

The condition bears a superficial resemblance to amyotrophic lateral sclerosis and to progressive muscular atrophy but differentiation is simple if the history, the paraesthesiae and the state of the arm reflexes are considered. It is suggested that so-called "traumatic" progressive muscular atrophy consists of undiagnosed cases of the order under consideration. The author vividly sketches the medico-legal implications of the condition.

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TRAUMATIC CEREBRAL FUNGUS

by J. E. A. O'Connell, *British Journal of Surgery*, 30, 201-212, January 1943

A cerebral fungus is a protrusion of the brain through a defect in all its coverings (scalp, skull and meninges) and must be distinguished from a cerebral hernia. In the latter the brain, although protruded through a defect in the skull, is still covered by the scalp and possibly by some of the meninges and hence is protected from direct infection. The infection, which inevitably follows on exposure of a fungus, leads to certain structural alterations in the brain substance. In the early stages the fungus appears as a pale, soft pulsating area covered by adherent flakes of lymph and superficial sloughs; later the surface becomes covered by granulation tissue and finally epithelialization occurs by centripetal spread from the margins. During these processes the subjacent cortical tissue becomes converted into scar tissue, and the epithelium is firmly adherent to it. There is no reformation of meninges and no reconstitution of the subarachnoid space.

The author, who is chief assistant to the Surgical Professorial Unit at St Bartholomew's Hospital and neurosurgeon in charge of one of the Head Injury Centres of the Emergency Medical Service, points out that the condition is a frequent complication of penetrating wounds of the head. It occurred in 11 (28%) out of 38 such patients whom he treated.

Penetration of the head by a high velocity metallic fragment may leave so small a hole that the brain is never exposed on the surface and the wound will heal rapidly, but when the trauma affects a wider area and the nervous tissue is exposed in the base of the defect, a cerebral fungus is constituted. If the superficial extent of the defect is relatively small, there will be no tendency to progressive protrusion even in the absence of treatment, but in larger defects protrusion of cerebral tissue occurs and becomes progressive unless checked by suitable measures. The tendency to progressive protrusion does not become manifest until an interval of 7 to 14 days has elapsed. Five of the author's 11 cases showed this tendency to protrusion and, of these, 3 showed evidence of a systemic reaction with inflammatory changes in the cerebrospinal fluid. A systemic reaction occurred in the non-progressive cerebral fungi in only 2 cases in which an attempt had been made to suture scalp over infected brain. None of the author's cases developed the complication of spreading suppurative encephalitis and only one had local brain abscesses. He attributes this in part to the use of sulphonamides, and in part to the free drainage of inflammatory products which takes place from the surface. Focal signs depend on the area of the brain which is damaged.

The intracranial pressure, assessed by lumbar puncture, is usually within the limits of normal (i.e. 100-180 mm. cerebrospinal fluid) but at times is above 200 mm. In the only patient admitted within 48 hours the pressure was 200 mm. cerebrospinal fluid and varied between 110 and

210 mm in subsequent weeks. The rachidian quotient—that is, the relationship between the volume of cerebrospinal fluid withdrawn at lumbar puncture and the resulting fall in intracranial pressure—shows a uniform variation. In the early stages the removal of a small quantity of fluid produces a marked fall in pressure, as the protrusion develops a considerably larger volume of fluid must be withdrawn to produce the same fall, and finally, as the stage of healing is reached, the quotient falls again. These observations suggest that there is an increase in the amount of cerebrospinal fluid in the cerebrospinal spaces when the fungus shows its maximum development. The cerebrospinal fluid is sometimes free from abnormalities but often shows evidence of an inflammatory reaction—pleocytosis and a raised protein content.

There has been much difference of opinion about the factors which produce the protrusion of the cerebral fungus and Magnant (1927) has classified the aetiological factors which have been suggested into two groups—"infective" and "mechanical". The "infective" theories postulate a raised intracranial pressure (which the author has shown not to exist in many cases) or a local oedema. Oedema, however, would be expected to be at its maximum shortly after the injury and to be subsiding after one to two weeks—i.e. at the time when the fungus first begins to protrude.

The most widely accepted "mechanical" theory is that of Leriche (1916), who postulates a strangulation of the protruded brain by the bony margins of the defect, the original protrusion having been occasioned by oedema. There is evidence to suggest, however, that the size of the fungus is determined by the size of the dural opening (as opposed to the size of the skull defect). Furthermore, it would be expected that a small opening would produce a more serious strangulation whereas large fungi are associated with large defects.

An alternative hypothesis is advanced which is believed to explain the known facts. In the first place there is always a localized dilatation of the lateral ventricle in relationship to a cerebral fungus. [A similar dilatation is frequently seen in other conditions associated with cerebral damage (e.g. after tapping of cerebral abscess and after closed head injuries with focal signs).]

Protrusion of the brain cannot occur without dilatation of the ventricle and it is suggested that it is the progressive ventricular dilatation which leads to the progressive fungation. This dilatation must not be confused with the ventricular deformation produced by traction of an overlying scar. Scar-tissue formation occurs only in the late stages of a cerebral fungus and can also have little bearing in the cases of a drained cerebral abscess or of a closed head injury.

The production of the cerebrospinal fluid is dependent on the capillary blood pressure within the choroid plexuses, and perhaps on the vital activity of its epithelium, while its absorption is due to osmotic and hydrostatic pressure differences between the fluid and the venous blood. But these are merely passive processes controlling the total volume of fluid. There appears also to be an active circulation of cerebrospinal fluid which is comparable with, and dependent upon, the cardiovascular circulation. Pulsations are visible in the normal brain when it is exposed, due to an increase of the total blood within the cranium with every cardiac systole. Considerable pressure-variations occur simultaneously within the ventricles and they can also be observed in the large cerebral subarachnoid channels. Respiration also plays an important part in causing slower but bigger pressure variations.

In ordinary circumstances, the brain volume rises during systole owing to expansion of the cerebral arteries, and there is an increased flow of cerebrospinal fluid from the choroid plexus. Hence there is a rise in intraventricular pressure which is believed to expel fluid from the lateral and third ventricles through the aqueduct into the fourth ventricle and thence through its foramina into the subarachnoid space. In the presence of diminished resistance of part of the ventricular wall the rise in pressure is partly expended in the normal manner and partly by dilatation of the ventricle into the damaged area. In the case of a fungus, the ventricular pressure will carry the exposed brain through the defect in its coverings. The fungation will tend to be progressive because the resistance of the brain tissue will diminish as it becomes progressively thinner. (The intraventricular pressure remains undiminished because, as the ventricular volume increases, more fluid is retained within it.) During the healing phase, granulation tissue gradually becomes converted into scar

tissue, which is firm enough to resist deformation from within.

In the treatment of the condition it is emphasized that fungation is avoidable in most instances. Every effort should be made to cover the brain with healthy scalp at the primary operation. If necessary, a scalp-flap should be swung over the defect and the denuded area of cranium should be Thiersch-grafted.

When a fungus is established, general and local chemotherapy are advised with a paraffin-gauze dressing over the wound in all cases. When progressive fungation is expected, or established, reduction in the intraventricular pressure and volume should be achieved by (i) raising the head end of the bed, (ii) mild dehydration by restriction of fluid intake to 1500 cm³ per diem and saline purgation or magnesium sulphate enemata, and (iii) removal of cerebrospinal fluid by lumbar puncture. The last is regarded as the most important: a sufficient volume of fluid must be removed to reduce the fungus to a deep concavity on each occasion and it must be repeated at frequent intervals until healing begins to increase the resistance to deformation of the ventricular wall. A gradual withdrawal over a period of a few hours is recommended.

The important sequelae of the condition are the occurrence of epilepsy in a high proportion, the existence of focal nervous signs, and the liability to brain abscess from latent infection.

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ACCIDENTAL HEAD INJURIES Prognosis in service patients

by C. P. Symonds & W. R. Russell, *Lancet*, 1, 7-10, 2/1/43

The authors, who as civilians before the War had published papers on the same subject, now report the findings in nearly 1,000 cases admitted to a Military Hospital for Head Injuries and carefully studied from the neurological and psychological point of view. Only head injuries due to accidents which also occur in civil life are considered in the present series, and gunshot wounds have therefore been excluded. Subsequent fitness for duty was assessed by means of a follow-up investigation. The factors which influence prognosis and the duration of treatment necessary are the principal problems considered.

There were 242 cases admitted in the acute stage, and these were relatively unselected. In those who survive, the duration of post-traumatic amnesia provides the best single factor for assessing the severity of brain damage. Where the duration of post-traumatic amnesia was less than 24 hours, 85% returned to duty successfully (i.e. had a satisfactory follow-up report). When the post-traumatic amnesia was of 1 to 7 days' duration the figure was about 70%, while when the amnesia exceeded 7 days, less than 40% returned to duty successfully. The duration of treatment (including full physical rehabilitation) was less than 3 months in 92% of cases, and in the majority less than 2 months.

The authors' experience has confirmed the view that preconceived ideas regarding the duration of rest in bed required and the degree of disability expected should be discarded. The patient who is free of symptoms may safely be allowed to progress quickly by graduated steps. The presence of a fracture of the skull does not delay recovery in most cases. Of the cases followed up at their Army or Air Force Units 84% were reported to be doing full duty efficiently.

Findings are also reported from 718 chronic cases who had been transferred to the special hospital to which the authors are attached, often owing to prolonged disability after a head injury, and these presented a very different problem.

Only about one-half returned to duty successfully even where the post-traumatic amnesia was of less than 1 hour's duration.

In this series of chronic cases, factors other than the severity of injury were found to influence prognosis. Among these a latent liability to mental disorder was particularly important. In cases with a personal or family history of mental disorder the proportion who became unfit for further service was twice as great as in the control group. In 111 cases of acute and chronic head injury in flying personnel of

the Royal Air Force, the prognosis for return to duty was four times as good as in all other cases in the series. The authors suggest that the reason for this is the careful selection in respect of freedom from predisposition to mental disorder of R A F flying personnel.

In conclusion they point out that physicians and surgeons usually have experience of patients with prolonged disability following head injury, especially after industrial accidents involving a claim for compensation. These cases give the profession a false view of the problem and a detailed study of a consecutive series of acute cases is helpful in that it presents the problem in its true perspective. Such a series shows that the duration of disability is usually short and that no harm comes from quick convalescence. Similar figures were obtained for civilian cases in a study made by one of the present writers (Russell, 1934) and more recently by Guttman (1943).

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THE PROGNOSIS IN CIVILIAN HEAD INJURIES

by E. Guttman, *British Medical Journal*, 1, 94-96, 23/1/43

In this paper from the Nuffield Department of Surgery and the Accident Service of the Radcliffe Infirmary, Oxford, the author points out that social and psychological factors, as well as organic damage, influence the prognosis in injuries received as a result of accidents. In previous publications on Accident and Rehabilitation Services, little reference has been made to head injuries, although these form a high proportion (30% at the hospital to which the author is attached) of all accident cases. At the present time social conditions in Britain are favourable and relatively uniform, and employers are prepared to facilitate gradual return to work. It seemed of interest, therefore, to study the prognosis of head injuries under such conditions.

The author's material is derived from 300 consecutive admissions, of which 255 were civilians and available for study, most of them road accident cases from a mixed urban and rural area. Ten patients (4%) died, and two were permanently incapacitated owing to cerebral damage. All cases were treated by encouraging early active movements. Lumbar puncture was performed only for diagnostic purposes.

Of the 245 non-fatal cases, over 80% were discharged within 2 weeks of admission including all *mild* cases (*i.e.* those with a post-traumatic amnesia of 1 hour or less), three quarters of the *moderate* cases (post-traumatic amnesia up to 24 hours) and half the *severe* cases (post-traumatic amnesia over 24 hours). The social classification of the cases was as follows:

	No of cases
Children under school age	12
School children	29
Housewives, excluding married women going out to work	25
Wage-earners, including married women going out to work	158
Owners of businesses	12
Not working, including chronic invalids	9

The average working time lost by 130 wage-earners of whom adequate records were available was approximately 8 weeks. It should be noted that all cases are included in these figures, whether they had concomitant injuries to other parts of the body or not. In *mild* cases the average loss of time was 4-5 weeks, in *moderate* cases, 5-6 weeks, and in *severe* cases about 9 weeks. In the most severe cases there was an average loss of about 14 weeks. Of eight patients who were off work for 26 weeks only two were incapacitated by cerebral damage. [The low incidence of headache in this series has been described elsewhere (Guttman, 1943).]

The author's findings in this series confirmed the value of the duration of post-traumatic amnesia as a guide to prognosis. From his analysis of the figures in cases in which injuries to other parts did not affect the results it can be said that a patient with a post-traumatic amnesia (PTA) of an hour or less should be fit for work within about 4 weeks,

with a PTA of up to 24 hours, within about 6 weeks, and with a PTA of up to 7 days, within about 9 weeks. These estimates are not valid for penetrating injuries, and the author recommends reference to a discussion by Cairns (1942) of this and other possible sources of error.

In all those cases with mild concussion who stayed off work for 7 weeks or more responsibility could be attributed to psychological factors. A short survey of another group of cases confirms the author's view that social and psychological factors have a great influence on the prognosis.

In conclusion the author emphasizes the need for psychological management in the early stages and facilities for psychotherapy and social after-care in convalescence and later.

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ELECTROENCEPHALOGRAPHY IN CHRONIC POST-TRAUMATIC SYNDROMES

by M E Heppenstall & D Hill, *Lancet*, 1, 261-263, 27/2/43

A much greater interest has recently been taken in the changes seen in the electroencephalogram (EEG) after head injury. Although the subject had previously been neglected, the increased number of head injuries seen in Britain as a result of the war has led to a progressive advance in knowledge in this field. Working at a neuropsychiatric centre of the Emergency Medical Service, the authors have been paying particular attention to the difference between the various disorders which may follow a head injury. In most cases the symptoms which persist after cerebral damage are partly due to organic change and partly to psychological factors, but in a few cases the syndrome is of entirely psychogenic or entirely organic aetiology. The authors therefore divided the 150 cases in the present series into a group of 87 with 'organic' states, of whom 29 had post-traumatic epilepsy, and a group of 63 with 'functional' states. The second group included anxiety states (21), depressive states (19), hysteria (14), psychopathy (7) and schizophrenia (2).

Fifty-eight per cent. of all these cases had an abnormal EEG, either at rest or after overbreathing. This figure agrees with those of other workers, notably with Williams (1941a, 1941b), who used a very similar standard of normality in a study of the effect of head injuries upon the EEG. One of the present authors (Hill & Watterson, 1942) has previously described the method and standards adopted. Abnormal records occurred nearly twice as often in the 'organic' post-traumatic states as in the 'functional'—63% compared with 37%. There was also a difference in the kind of abnormality, as in the functional states a diffuse abnormality was usually found throughout the cerebral hemispheres, while in the organic states the abnormality was often focal—54% compared with 16%.

The observation of Williams that the incidence of electroencephalographic abnormality is not affected by the time after the injury, but that it is directly related to its severity and to the length of the post-traumatic amnesia, was confirmed. This positive correlation with the severity of trauma was particularly significant in the cases with focal abnormality. The present authors also found that the incidence of electroencephalographic abnormality was greater in the 99 subjects with a normal personal history than in the 51 with an abnormal personal history, which included neurosis or psychosis—60% compared with 37%. This again was most evident in the patients with focal lesions. An abnormal family history, including evidence of epilepsy, psychosis, severe neurosis, mental defect and psychopathic personality in first degree relatives was obtained in 53 patients. The incidence of abnormal EEGs in these (51%) was not significantly greater than in those with a good family history (48%). Again, when the EEG abnormalities were divided into focal and general, there was a significant difference between the 'organic' and 'functional' groups, for in those with an abnormal family history, 26% had a focal and 74% had a diffuse disorder, while in the others, 54% had focal and 46% had diffuse abnormalities.

Many workers have now shown that the incidence of diffuse changes in the EEG is higher when behaviour disorders

are present than it is in normal controls. This is so when the abnormal behaviour is caused by a psychoneurosis, a psychosis, a psychopathic state, or by epilepsy. Williams stated that the EEG abnormality in such cases indicates an inborn constitutional defect which may find expression as epilepsy or as a behaviour disturbance, such as a constitutionally determined neurosis, or as psychopathy. The present authors agree with this view, but observe that it seems, from the results summarized above, that a focal abnormality in the EEG is evidence of an acquired lesion, while a diffuse one may indicate an inborn constitutional defect, even after a head injury. In these cases the post-traumatic syndrome is consequently mainly psychogenic. It follows that the presence of diffuse abnormalities in the EEG in post-traumatic states does not necessarily indicate the presence of organic cerebral damage.

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TREATMENT OF HEAD WOUNDS DUE TO MISSILES ANALYSIS OF 500 CASES

by P. B. Ascroft, *Lancet*, 2, 211-218, 21/8/43

Major Ascroft was in charge of a Mobile Neurosurgical Unit in the Middle East during two years of the fiercest fighting there. He has recorded the results of his experiences in this paper, which is of first importance to everyone concerned with the treatment of battle casualties. Methods designed to suit the conditions of mobile warfare are described in great detail and can be only inadequately summarized here. The report is based upon the results of operations in 516 cases. The final results were that 71% of cases returned to duty, while 9% died. Figures are given showing the relationship of severity of injury to prognosis. This was worst when the dura was penetrated, as in these circumstances only 55% returned to duty, while 15% died.

Special difficulties are encountered in attempting to treat wounded efficiently during the course of modern mobile battles. Against these difficulties must be set the peculiarities and function of the brain and its coverings which influence the behaviour of head wounds and their treatment. These are

- i The scalp is richly supplied with blood, it has considerable resistance to infection, and heals well.
- ii Spreading osteomyelitis of the skull is very rare (no instance in this series of more than 400 compound fractures).
- iii The intact dura is a powerful barrier to the spread of infection, and the meninges as a whole have considerable powers of localizing infection.
- iv The tissue of the brain resists infection well, provided that the products of trauma and inflammation are not allowed to accumulate under pressure.
- v Continued exposure of the brain in an open wound is always harmful, and is always associated with some degree of infection.

In view of these considerations, some delay before operation is not so harmful as it might be with wounds elsewhere, while closure is very desirable. Three further important points are

- vi Organic damage to the brain is irreparable, and even the gentlest surgical manipulations are damaging in some degree.
- vii Surgical manipulations within the skull cannot be carried out effectively without preliminary x-rays and special apparatus, especially an efficient mechanical sucker.
- viii "Every scalp wound, no matter how trifling, is a potential penetrating wound of the skull" (Cushing in 1918).

First aid and resuscitation. The surgeon must assess (a) degree of shock, (b) depth of coma, (c) nature of the head wound, (d) nature of other injuries. The wound should be superficially cleaned, dusted with sulphanilamide powder, and bleeding should be controlled. Shock, when present, is usually due to loss of blood and will require a large transfusion. Contrary to general belief, morphine is the best sedative in these conditions.

Evacuation. The results of primary operations at the base hospital, three days after the injury, were found to be as good as they are if carried out within 8 hours of the injury in the

forward areas. Subjects of head injuries usually travel well, so that it is best not to retain head cases in the forward areas unless there is (i) severe shock, (ii) need for urgent surgery, either because of the local condition, e.g. cerebral compression, or because of injuries elsewhere, (iii) no reasonable hope of reaching a special centre within 2-3 days. If interference is necessary at the forward area the operation should be modified. There should be an open toilet of the wound with thorough cleaning and excision of dead tissue, removal of loose bone and enlargement of the hole in the skull. The dura should not be touched, sulphanilamide should be introduced, and the whole area should be left open, and simply covered by a sterile dressing.

At the base hospital. First there is a brief examination (i) to determine the need for resuscitation, (ii) to establish a base-line by which to judge progress, for the better or the worse, especially with regard to the level of consciousness, (iii) to decide the priority for operation. There should be an immediate x-ray in order, by the presence of bone fragments or missiles, to find if the dura has been penetrated. This practice is strongly recommended immediately after clinical examination, one of the aims of which is to measure the state of consciousness. Notes should be made immediately, for it is important to observe any change of consciousness with the passage of time. The wound should be examined very carefully, for it may not be so trivial as it appears, or there may be many unsuspected small wounds. However small they are, it should never be assumed that they are not deep. Leakage of cerebrospinal fluid from the wound is a bad sign as it indicates free communication with intracranial contents. Eight per cent of all wounds completely traversed the cranium, and they usually had a large exit. Examination for other wounds should be detailed, as their neglect may cause death when the head wound has been satisfactorily treated. Lumbar puncture before operation is not important, but it is useful afterwards for judging alterations in the state of the patient.

The anaesthetic of choice is sodium pentothal, 0.5 g in a 5-10% solution, maintained by a 1% solution. The operation begins with very thorough preparation of the wound after anaesthesia. In these conditions of surgery, extra time in preparing the patient and the wound is well spent. Transfusion should be started early. The first stage in the operation is to inspect for fractures and then to excise narrowly all dirty and grossly damaged or coagulated tissue. Destruction is often wider below the skin than on the surface.

The treatment of bone depends upon the fracture. A depressed fracture always tears the pericranium and, unless there is a simple linear fracture, the area of bone should be excised conservatively to prevent infection. Ascroft has found that a gap of less than 3 cm is soon filled with fibrous tissue. He describes in detail the management of special skull fractures with diagrams. The dura is usually penetrated if there has been a hole in the bone, however small this is. The intact dura should never be opened unless there is a threat to life from a subdural clot. If it seems whole, leave it alone, if not, simply tidy it up, but when the brain is penetrated a more radical approach is needed.

A penetrating wound usually carries a shower of small bone fragments into the brain, and in half the cases a missile, which is found by x-ray, is there too. If the bone fragments are not removed, there will probably be abscess formation, as only a small proportion of fragments removed are found sterile on culture. Consequently all debris and badly damaged brain should be removed and the softened tissues sucked away. When the plug of blood clot is removed the damaged brain will usually ooze out, but this can usually be encouraged by making the patient strain. If the missile is not readily accessible it should be left untouched, for it is usually sterile. Good haemostasis should be secured and it has been Ascroft's practice to dust the wound liberally with sulphathiazole. He has used a cream in deep cavities and tracks, and has never seen epileptic fits follow this treatment.¹ The treatment of special conditions like extensive superficial wounds is discussed. The dura should not be closed because the track is usually infected, and even so, 12% of primary operations at the base hospital give rise to abscess formation, while if the dura is closed this proportion is higher, especially

¹ [This refers to the epileptogenic properties of sulphathiazole, when applied to the brain. These effects are confined to application to undamaged cortex. See BMB 55—Ed.]

if the wound is a few days old The wound should be drained deeply with a corrugated rubber drain, but the scalp, if possible, should be closed up to the drain It is unwise to try to pull the edges of wounds together when there has been much tissue loss, for the scalp will probably slough, especially if it is infected

The post-operative management is important, and needs a large staff, for the comatose require much nursing, and the others are restless and difficult For 50 cases Ascroft thinks at least 6 fully trained nurses, 12 nursing orderlies, and 8 recovered and co-operative patients are needed to help Fluids should be forced, for the patients are usually dehydrated, and there should be one orderly whose sole duty it is to attend to this At this stage Ascroft uses as a sedative either paraldehyde, intravenously or by mouth, or morphia The return to activity is encouraged by occupation in the hospital, and he finds that most recovering patients are very co-operative Failure to show the usual will to get better probably implies the onset of complications

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GUNSHOT WOUNDS OF THE HEAD IN THE ACUTE STAGE
by H Cairns, *British Medical Journal*, 1, 33-37, 8/1/44

This paper reviews the work of the British Army's neurosurgeons dealing with gunshot wounds of the head in the Middle East and North Africa The army neurosurgical unit was designed to be mobile, self-contained, and able to work as a casualty clearing station or general hospital, but it did not have its own x-ray equipment, nor was it designed to nurse or feed its patients, its vehicles providing power for diathermy, suction pumps, and operating-theatre lights The first unit, with Major Henderson and Major Challis, was captured in France in 1940, and units under Majors Ascroft, Eden and Schorstein went later to the Middle East region

At first it was found that a unit working in the forward area failed to collect an adequate number of head wounds, and it was placed further back with a general hospital After the fall of Benghazi, as a result of the narrowing of lines of communication, it was practicable for Eden to divide his unit, leaving one section in a general hospital at Tripoli while he, with the other section, went forward to an advanced casualty clearing station The divided sections of this unit were thus able to filter out nearly all the cases of head injury occurring in that battle area, the more serious cases were operated on by the forward section, and were sent back for later care Other casualties were passed directly back to the rear section of the unit

In this way 293 cases were operated on, 188 of them within the first 24 hours after wounding The advantage of this organization was seen in the high proportion of primary wound-healing, which reached the remarkable figure of 90 % Schorstein was less favourably situated, although he estimated that eventually he was obtaining about 75 % of the head wounds of the First Army, but he was unable to retain cases for long and it has been difficult to follow up the results

Non-penetrating injuries, i.e. wounds involving the scalp and the bone without laceration of the dura mater, have had practically no mortality, there being only 3 deaths in a total of 459 cases Emphasis is again placed upon the need for careful surgical treatment of scalp wounds The careless excision of such a wound may lead to prolonged suppuration and as it is not possible for neurosurgeons to deal with all such wounds it is incumbent upon the general surgeon to follow their meticulous methods

The results of penetrating brain injuries are given in the table together with some available German figures and the figures of Cushing in 1918 Ascroft was working at the base, and the low mortality (15 %) is an indication of his distance from the firing line as compared with the 23.6 % of Eden, who was well forward A high percentage of Ascroft's cases developed brain abscess, with a mortality-rate of only 25 % Although the cases in which Ascroft performed the primary operation were considerably older at the time of operation than those operated on by general surgeons in the forward area, yet brain abscess was only one half as frequent In Cushing's cases there was also a high incidence of abscess but the abscess developed earlier and fatal meningitis usually supervened rapidly The incidence of brain abscess in Eden's

cases was considerably lower than in Ascroft's, to be explained by the fact that Eden got his cases at a much earlier stage and before they had been operated on by the general surgeons

TABLE
PENETRATING BRAIN INJURIES

Surgeon	Total head wounds	Penetrating wounds				Remarks
		Total	Mortality (% in brackets)	Primary healing (%)	Deaths from infection (%)	
Ascroft (1943)	516	292	44 (15.0)	67 (fresh) 22 (old)	10.8	Base
Eden (1943)	325	102	24 (23.6)	65.5	3.7	C.C.S.
Schorstein	—	112	15 (13.4)	67.6	Low	Forward base
Sorgo (1942)	—	29	13 (44.8)	—	34.5	—
Cushing (1918)	250	133	60 (45.1)	Ca. 70	36.5	C.C.S.

There were 73 consecutive cases of brain wound flown from El Alamein to the base where Ascroft operated on them within 24-48 hours of injury, and in these the operative mortality was 25 %—a figure much the same as Eden's The healing of the wounds has been roughly similar among all the units Cairns' comment on these figures is that if head cases can be segregated at the level of the casualty clearing station, and can there be radically operated on within 24 hours of injury by a fully equipped team trained in war neurosurgery, there is considerable improvement in results, and the complication of brain abscess or of other forms of intracranial infection can be almost although not entirely eliminated

Little work has been done on the bacteriology of head wounds Major Scott-Thompson examined material from 36 cases in Sicily, finding the predominant organism to be *Staph aureus* (23 cases), other organisms being haemolytic streptococcus, pneumococcus, *Staph albus*, coliforms and clostridia Findings at operation and bacteriological examination of material suggest that infection probably develops in the superficial part of the wound, and only secondarily spreads deeply into the brain Although the Russians have recently reported that a large proportion of deaths from brain wounds are due to pathogenic anaerobes, this has not been the experience in the Middle East theatre of war

Operative technique is briefly described, and the insufflation of a surgically clean and dry wound with sulphathiazole powder has been practised without causing epilepsy¹ Where a previous operation has been carried out inadequately and bone chips still remain in the brain, it has been the practice to reoperate radically and evacuate the brain debris and bone chips Wounds of special regions, and the value of an osteoplastic flap in certain cases, are discussed Although chemotherapy as a prophylactic measure has been extensively used, its value in controlling the local wound-infection is still in doubt

Penicillin was used in a selected series of cases 3 or more days old, the wound was excised and closed with an indwelling fine rubber tube, into which calcium-penicillin solution (250 units per cm²) was instilled twice daily for 4 or 5 days Excluding two moribund cases which were not operated upon, 23 wounds from 3 to 12 days old were thus treated, at operation 13 were purulent to the naked eye, and 4 presented a cerebral fungus Three patients died, 1 from an intracranial clot and 2 from brain abscess Primary wound healing occurred in 6 of the 20 survivors In 17 other cases of non-penetrating injury 1½-16 days old, there was satisfactory healing in all but 2.

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GUNSHOT WOUNDS OF THE FRONTO-ORBITAL REGION
by J Schorstein, *Lancet*, 1, 44-47, 8/1/44

The author, a major in the Royal Army Medical Corps and officer-in-charge of a mobile neurosurgical unit, gives

¹ [See footnote to *BMJ* 638—Ed.]

details of 10 cases of gun-shot wound involving the fronto-orbital region of the skull. He operated personally on 8 of these, of which 1 died, and 1 could not be traced. The 2 remaining cases came under his care after operation elsewhere, no further radical procedure was undertaken, and they both died of spreading infection in the brain. In 3 of the 8 personal cases, the laceration of the dura mater was entirely closed with fascia-lata graft, and the overlying skin wound closed. In 4 of these cases it was not possible to do this, and the brain wound and the cavity resulting from careful excision of the paranasal sinuses and orbits were packed with soft-paraffin gauze.

In the 8th case, a combination of fascial graft to the dura mater and packing of the superficial wound was carried out.

The author discusses the principles involved in dealing with battle injuries of the head, and in particular those wounds involving the fronto-orbital region. Complete closure of the intracranial cavity by a fascial graft, and of the overlying integument by two-layer suture, is the method of choice, but this primary closure of wounds depends entirely upon a meticulously careful excision. If this excision is carelessly or incompletely performed, then primary closure is doomed to failure. In fronto-orbital wounds, sepsis is particularly liable to develop owing to the fact that the lepto-meningeal spaces are thrown into communication with the paranasal sinuses and thereby the upper respiratory tracts, and wound closure may be difficult because of the involvement of the orbit. He emphasizes the need for total removal of devitalized tissue within the brain and the orbit, the complete removal of all the mucous membrane lining the paranasal sinuses which may be involved, and the removal of bony septa and walls, so as to form one continuous cavity without any pockets.

Although grafting of the dura mater and primary closure of the skin is the method of choice, yet in certain cases this may not be possible, for it is a time-consuming operation and the patient's condition may contra-indicate it. Loss of skin may necessitate the fashioning of adequate skin-flaps for primary suture, and this may not be considered advisable for fear of producing facial distortion. It was for such reasons that the vaseline gauze pack was first employed in this series, and it proved so successful that further cases were similarly treated. It is quite clear that this forms a valuable alternative method, and where time presses it may still have application elsewhere in the head. The paper is a valuable one, especially as the case records are reported in detail.

where in the body create difficulties in specialized war surgery, in some cases the other wounds were treated by the unit, and sometimes with the help of general surgeons. The frequent association of wounds of the eyeball made liaison with an ophthalmic surgeon necessary.

Pre-operative measures consisted of careful and complete neurological examination, and radiography of the skull. Lumbar puncture was not considered to give sufficiently valuable information to justify its routine use. The importance of careful shaving of the head is emphasized, and it was usually completed by the surgeon himself, the orderly always wore a mask so as not to add to the wound flora. The anaesthetic most commonly used was local infiltration, following a basal narcosis of omnopon and scopolamine, but when the eyes or ears were involved, or if the patient was very restless, endotracheal cyclopropane supported by pentothal was favoured.

It was Major Eden's firm belief that there is no useful first-aid operation in the treatment of brain-wounds, and that the initial operation should be the final and complete one, "the surgeon first operating on a head wound makes or mars it". Failure to obtain primary union, or the inadequate removal of indriven bone fragments, all too frequently imply the vicious circle of cerebral fungus, abscess, and meningitis. The first step was adequate excision of the contaminated scalp through all layers, including any side lacerations and undermined areas, but preserving every available portion of healthy skin. The edges of the bone defect and all loose fragments of bone were removed, but extensive stripping of the surrounding bone of its periosteum was avoided, and fragments of bone with sound periosteal attachments were retained. Only obviously contaminated tags of torn dura were excised, the wound in the brain was explored and all indriven bone fragments, clot, and pulped brain were removed by gentle suction and irrigation, but the metal foreign body was removed only in cases in which it presented in the wound. The complete closure of the scalp by accurate two-layer suture without tension was considered essential, and in order to obtain this, the wounds were extended as necessary in order to mobilize the skin, it was never found necessary to leave bare areas elsewhere in the scalp. Insufflation with sulphathiazole powder was performed as a routine, and the wounds were drained for twenty-four to forty-eight hours. A fascial graft was used only in a few cases of paranasal sinus wounds. Where the missile had passed through the eyeball into the brain the orbital contents were removed, and the lids sutured. In several

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I MOBILE NEUROSURGERY IN WARFARE EXPERIENCES IN THE EIGHTH ARMY'S CAMPAIGN IN CYRENAICA, TRIPOLITANIA AND TUNISIA
by K. Eden, *Lancet*, 2, 689-692, 4/12/43

II MOBILE NEUROSURGERY IN WARFARE EXPERIENCES IN THE EIGHTH ARMY'S CAMPAIGN IN CYRENAICA, TRIPOLITANIA AND TUNISIA
by K. Eden, *British Journal of Surgery*, 31, 324-328, April 1944

The late Major Eden describes the work of his neurosurgical unit during the rapid advance of the Eighth Army in North Africa. At first the unit worked with a forward casualty clearing station, the cases after operation being evacuated by air to the base. Eventually this journey became too prolonged, and the unit was then divided so that one half was left at a hospital on the lines of communication to act as a changing post, at the same time collecting cases missed by the mobile team, while the other half of the unit continued to advance in the forward area. In addition to the standard equipment a derelict 10-ton motor-coach captured from the Italians was adapted to form a self-contained mobile operating theatre. A corridor connected the theatre with a tent in which the cases for operation were sorted, and the necessary pre-operative investigations and treatment were carried out.

The selection of cases was important and in general the open brain-wound took precedence, many of the simple depressed fractures and scalp-wounds being evacuated by air to the base team. On the other hand, unconscious cases were given a lower priority, as coma was found to be a grave prognostic sign in brain-wounds. Associated injuries else-

CLASSIFIED RESULTS OF PRIMARY OPERATIONS

Type of case	No. of cases	Deaths	Healing 1st intention	Infected wounds *	Complications
Scalp wounds	139	—	135 (97.1%)	4	1 extradural abscess
Fractures (dura intact)					
Depressed	45	—	41	4	Sequestration, 1
Fissured	7	1	5	1	—
Sagittal sinus injury	2	—	2	—	—
Air sinus and eye wounds	9	—	5	4	Sinusitis, 1, rhinorrhoea, 1
Face wounds	1	—	1	—	—
Ear wounds	5	—	4	1	Mastoiditis and subcutaneous abscess, 1
Total	69	1	58 (84.1%)	10	
Open brain wounds					
Perforating brain wounds (metal in-driven)	51	12	35	7	Cerebral fungus, 4, meningitis, 4, cerebral abscess, 1, fits, 1, cerebrospinal fluid leak, 2
Compound fracture (in-driven bone only)	24	5	19	3	Cerebral fungus, 2, meningitis, 1
Compound fracture (dura torn)	10	—	9	1	Fits, 2
Air sinus and eye-brain wounds	7	2	5	1	Pulmonary embolism, 1, rhinorrhoea, 1
Ear-brain wounds	3	2	1	—	Mastoiditis, 1
Face-brain wounds	1	—	1	—	—
Sagittal sinus brain wounds	6	3	3	1	Sagittal sinus thrombosis, 1
Total	102	24 (23.6%)	73 (71.6%)	13	
Grand total	310	25	265	27	

* Including wounds left open.

cases in which the ear had been implicated, mastoidectomy was later necessary. Sagittal-sinus injury was repaired by silk sutures reinforced with muscle grafts, and no case of fatal haemorrhage occurred.

As most of these patients had to travel hundreds of miles by air, a firm head-dressing which could not be removed by a restless patient was necessary, and the plaster cap was found most reliable. On it were inscribed the brief details of the injury, the site of the wound, and the time for removal of the drain and stitches. In all cases in which the wound involved the brain, sulphadiazine was given (3 g 4-hourly for 48 hours, and then 3 g 8-hourly, or 5 g 12-hourly intravenously in an unconscious patient). For relief of restlessness paraldehyde (3 drachms [about 10.5 cm³] orally, 8 drachms per rectum or 3 cm³ intravenously) or soluble phenobarbitone (3 grains [about 0.2 g.] intravenously) were found to be the most reliable. Comatose patients were fed through a nasal stomach tube. Provided progress was satisfactory, the cases were evacuated from the forward team on the second or third day after operation, and contrary to earlier belief they travelled well.

The cases are analysed and tabulated in detail, and one of them is described in full. In the majority of the cases operation took place within 24 hours of wounding, and in these primary healing was obtained in 92%. Even in those in which 3 days elapsed before operation, this figure did not fall lower than 87%. It is instructive to note the comparison between cases primarily operated upon by the unit, and the cases reaching the base after primary operation had been performed in the forward area by general surgeons. In the latter series there were 13 cases of scalp wounds in which healing by primary union occurred in approximately only one-half, and there were 24 cases of brain wound in which primary union occurred in approximately one-fifth, and in this group there were many cases of cerebral abscess, fungi, encephalitis, and meningitis. These figures alone demonstrate the value of the neurosurgical units and the justification for their formation.

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RECOVERY OF SPATIAL ORIENTATION IN THE POST-TRAUMATIC CONFUSIONAL STATE

by A. Paterson & O. L. Zangwill, *Brain*, 67, 54-68, March 1944

In this paper from the Brain Injuries Unit, Edinburgh, the authors report in detail two cases of post-traumatic confusion, and show how the recovery of correct spatial orientation may in severe cases be a gradual process. The fluctuating disorientations which precede correct orientation are analysed in detail, and a characteristic defect of judgment or thinking is shown to occur. Orientating data often appear to patients in this state to conflict, and facile and unrealistic reconciliations of the apparent conflict occur.

Different types of rationalization are discussed and three forms are distinguished. In one type there is a facile verbal identification of one place name with another. In another type the places, some distance apart, are regarded as contiguous. In a third type the solution is reached by the mechanism of reduplicative paramnesia, the patient argues that he is in a place A (his "true" locality) but was shortly before at place B (the content of the disorientation). Some cognitive factors underlying disorientation are considered and their relative significance is assessed. Special attention is given to impaired perception, memory-retention defect, and retrograde amnesia. The part played by a dominant affective attitude in provoking and maintaining disorientation is illustrated in one case.

The similarity of this phenomenon to hysterical reactions and to the delusions common in the primary psychoses is briefly considered.

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A PSYCHOMETRIC METHOD OF DETERMINING INTELLECTUAL LOSS FOLLOWING HEAD INJURY

by W. R. Reynell, *Journal of Mental Science*, 90, 710-719, July 1944

About 15-20% of moderate or severe head injuries are followed by persisting intellectual impairment. The tests

described by Major Reynell are based on the well-established assumption, to which the work of Babcock (1930) has largely contributed, that vocabulary, general information, and powers of comprehension suffer less in deterioration than such capacities as reasoning-ability, attention, recent memory and "relational thinking".

The first group of intellectual abilities is measured by the "A" series of tests consisting of a 42-word vocabulary, 25 questions of general information, and 10 questions designed to test general comprehension. The second group is measured by the "B" series consisting of 10 arithmetical tests, digit repetition, forwards and backwards, and 12 pairs of words designed to test "relational thinking"—or seeing abstract relationships. The tests were based on the Wechsler (1941) series.

The intelligence-quotient was calculated for the A and B series separately, and if they differ by 10 points or more, the result is regarded by Major Reynell as being positive for intellectual loss.

The longer the period between the head injury and testing, the greater will be the significance of a positive finding.

The difference of 10 in intelligence-quotient is arbitrary, but it was found that 80 of 100 cases giving a positive result, 2 months or more after the head injury, were discharged from the Army as unfit on general clinical grounds. Eighty per cent of cases showing a negative result were returned to duty.

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DISCUSSION ON DISORDERS OF PERSONALITY AFTER HEAD INJURY

by A. Paterson, W. R. Reynell & M. Kremer, *Proceedings of the Royal Society of Medicine*, 37, 556-566, August 1944

Paterson regards personality as the pattern of behaviour which the individual exhibits in adjusting and reacting to his environment. Cognitive as well as affective and dynamic factors are involved. The former are often artificially divorced from the latter, and this separation is accentuated by the different ways in which they are acquired. The cognitive skills often develop through a period of standard education, whereas the acquisition of the emotional and temperamental attitudes is often haphazard and unintentional.

The confusional state following head injury may be regarded as the acute breakdown of the personality pattern, and its detailed study can throw important light on the subsequent chronic personality change, which is often difficult to assess if studied in isolation. The pattern of the confusional state after head injuries depends upon the distribution of the confusional damage on the different parts of the brain, and upon the impairment of the function, which is often relatively well localized, of those parts. It follows that the late disorders of personality also derive their character from the distribution of the confusional damage to the brain. Each case of personality-disorder following head injury is an individual affair and should be assessed as such. Routine psychological tests to assess post-traumatic personality change must be used with discrimination. They were originally introduced to measure abilities in normal intact individuals and are not clinical tests derived, as other tests are, from the detailed study of the pathological phenomena. Their indiscriminate use may lead to distortion of the actual clinical findings and may impede further analysis.

The changes in the emotional and temperamental attitudes following head injury are often exaggerations or caricatures of previous tendencies in the same direction. There is a loss or impairment of the previous standards of behaviour. This loss deprives the patient of the ability to measure his post-traumatic personality.

Reynell describes a differential testing procedure designed to provide a quantitative index of intellectual impairment and to help in distinguishing organic from functional sequelae of head injury. His procedure adapted from Wechsler, consists of 3 tests which are appreciably affected in deterioration with cerebral injury (A Series) and 3 which fall off with traumatic intellectual loss (B Series). A discrepancy of 10

or more units between the Intelligence Quotients corresponding to the two series is considered significant. The test battery, which can be administered in 20–30 minutes, was given to 1500 cases of head injury and the results were followed up in 500. It was found that 25 % of 800 cases tested 2 months or more after the injury displayed an average difference of Intelligence Quotients of 14 between the A and B Series. Of those followed up, 73 % were discharged from the army and 80 % of an equal number of cases presenting no such evidence of intellectual loss were returned to duty. These disposals were made on clinical grounds alone, but their correlation with the test findings is evidently high. Reynell also finds that 9 out of 10 cases with personality-change show intellectual loss, but that a majority of those with intellectual loss alone show no striking personality-change. Of a control group of psychoneurotics (without head injury), 92 % gave negative results on differential testing, hence the method can be of help in differential diagnosis. Reynell strenuously denies that assessment of post-traumatic personality changes can be reduced to psychometric testing, but urges that it is often difficult to attain a just appraisal without the aid of such tests.

Kremer, in reviewing 2,700 cases of head injury admitted to a military hospital, was impressed by the disagreement among the most competent observers as to the presence or absence of personality-disorder in particular cases. The discrepancy appeared to arise from the difficulty in the correct appraisal of the pre-traumatic personality, but there were cases in which personality-change would be accepted by all observers. Accepting the length of the post-traumatic amnesia as a criterion of the severity of the injury, Kremer found that the chance of discovering post-traumatic personality change was greater with more severe injuries. Of 156 cases with post-traumatic amnesia of more than 7 days, 37 (24 %) showed personality-change confirmed by all observers. The changes themselves could be classified roughly into those showing disinhibition of various kinds, and those showing apathy and diminished initiative. The change may take the form of psychoneurotic symptoms. In some cases, the contusion of the brain is a true aetiological factor in the production of these symptoms, in others, where the reaction to the head injury is similar to the reaction to an unhappy love affair, or to a broken leg, the symptoms or personality change can be spoken of as post-traumatic only in the chronological as opposed to the aetiological sense.

Intracranial Disease

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ANTERIOR AND POSTERIOR FOSSA CEREBRAL TUMOURS · Clinical study of 122 cases

by G J Dixon & G Fitzgerald, *Lancet*, 2, 595–596, 21/11/42

The difficulty of deciding whether a cerebral tumour lies in the anterior or posterior fossa has been stressed by various writers (Hare, 1931, Gordon, 1934, Jefferson, 1939), who noted that the symptoms produced by anterior fossa tumours may closely resemble those of lesions in the posterior fossa. Observation of several cases which illustrated this difficulty led the present authors to analyse the clinical symptoms of 122 cases of proven anterior and posterior fossa tumours in the National Hospital, London, between January 1938 and October 1940. Fifty-six of the cerebral tumours were localized in the anterior and 66 in the posterior fossa.

The grasp reflex in 9 % of the anterior group, and cerebellar ataxia in 44 % of the posterior group, were the only unequivocal signs.

Nystagmus was seen in 10 % and epileptiform fits in 41 % of the anterior group, the incidence of similar findings in the posterior group was 64 % and 8 %. Mental change was so common in both the anterior (75 %) and posterior (25 %) groups that the authors do not think it should be considered of value in localization.

In 23 % of the anterior fossa group and in 10 % of the posterior fossa group there were no localized physical findings.

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PAROXYSMAL AND POSTURAL HEADACHES FROM INTRAVENTRICULAR CYSTS AND TUMOURS

by W Harris, *Lancet*, 2, 654–655, 18/11/44

Up till 1936 accounts of only 49 cases of tumour or cyst in the third ventricle had been published. The author describes two further cases and mentions two others. In many instances no symptoms and signs other than those of hydrocephalus have occurred. Sudden death has been common. Probably such tumours and cysts are more common than the published records indicate. Paroxysmal headaches with sudden onset and often equally sudden disappearance have been recorded in most of these cases, but more characteristic is the sudden relief of the pain on change of posture. This was observed by Fulton & Bailey (1929) and by Stookey (1934).

Pedunculated tumours growing from the wall of the lateral ventricle may be ependymal in origin, the tumours growing in the third ventricle are often colloid cysts. These cysts are thought to be paraphyseal in origin and grow downwards from the anterior end of the roof of the third ventricle (Sjovall, 1909, Bailey, 1916, McLean, 1936). The cysts are liable to block one or both of the foramina of Monro, and changes in posture are likely to shift their position slightly so that sudden relief of headache due to escape of fluid from the distended lateral ventricle is a characteristic symptom. Tumours more posteriorly placed in the third ventricle tend to cause the signs and symptoms of a lesion of the anterior colliculi and the hypothalamus. The author's two cases were the following.

Case 1 Male, aged 48, with a 12-months history of recurrent attacks of vertigo and sagging of the legs. There were also severe paroxysmal headaches of sudden onset and disappearance, lasting for a few minutes. Memory was much affected. Examination revealed papilloedema and a raised pressure of cerebrospinal fluid. Ventriculography disclosed a globular filling-defect in the upper and anterior part of the third ventricle. At operation, a cyst was removed by excising a circle of right frontal lobe and entering the lateral ventricle. Recovery was uneventful but the memory remained uncertain.

Case 2 Female, aged 22, with a 2-years' history of severe intermittent headaches, which had become continuous for the previous 3 weeks. They were liable to start and disappear suddenly and she could sometimes stop them by throwing her head back. Examination revealed severe papilloedema. The pressure of cerebrospinal fluid was raised. Ventriculography disclosed an enormously dilated left lateral ventricle bulging slightly across the mid-line. The third ventricle was not filled. A small circle of left frontal lobe was excised, the ventricle was entered, and a colloid cyst, which was protruding through the left foramen of Monro, was removed. It contained thick, creamy fluid. She made a good recovery and returned to work.

The writer emphasizes the fact that change of posture may cause a sudden change in intensity of the headache. Weisenburg (1910) first described intermittent sudden loss of vision dependent on changes of posture in cases of third-ventricle cyst. The headaches in these cases may precede other symptoms, such as vomiting, dizziness, fainting, sudden falls from weakness of the leg, etc., by as much as 10 years. The sudden weakness of the leg may suggest a diagnosis of cataplectic attacks in narcolepsy, but the characteristic somnolence is absent, while the hydrocephalic symptoms point to a diagnosis of intracranial tumour. Hysterical features may characterize other cases.

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THE IMPORTANCE OF AIR ENCEPHALOGRAPHY IN INVESTIGATION OF EPILEPSY OF LATE ONSET

by J McM Mennell & C Worster-Drought, *British Journal of Radiology*, 17, 286–288, September 1944

Two cases of epilepsy are described. Neither of them showed any abnormal physical signs but their age and history was

sufficiently unusual to warrant air encephalography. In both cases this revealed abnormalities which could only be due to a tumour, which was later found at operation to be inoperable. Decompression and radiotherapy improved the condition and prognosis. Encephalography was carried out by the lumbar route.

Case 1. Female, aged 30. Nineteen months before admission to hospital, when 4½ months pregnant, was frightened by a spider, she ran out of the room screaming and remained in terror for some hours. A month later she began to scream and had a fit, which was followed by abortion. The fits recurred daily for a week. She was then free for 6 months, when she again became pregnant and one day lost consciousness in the street and again aborted. The fits recurred with varying frequency, often at the time of her menses. They were preceded by a choking sensation, numbness and twitching of the right side of the mouth, a hot and cold sensation in the right side of the head and neck, and "pins and needles" down the right side of the body. She was unable to speak before some attacks, but did not lose consciousness. No abnormal physical signs were present. x-ray of the skull, pressure and constitution of cerebrospinal fluid were normal, Wassermann reaction negative. Electroencephalogram showed no abnormality. Air encephalography revealed a normal filling of the right lateral ventricle, which was pushed over to the right. Only a small amount of air could be seen in the left lateral ventricle, which was also displaced, as were the third and fourth ventricles. Operation disclosed flattening and widening of the inferior end of the post-rolandic convolution, indicating a deep-seated neoplasm. She was given a course of deep x-ray therapy and anti-convulsant treatment.

Case 2. Female, aged 34. Three months previously she had a fit lasting eight hours, followed by focal attacks affecting the right side of the body. There was also a burning sensation present on the whole of this side. There were no abnormal physical signs present. x-ray of the skull, pressure and constitution of cerebrospinal fluid, were all normal, and the Wassermann reaction negative. Air encephalography showed poor filling of the anterior horn of the left ventricle, which appeared pushed to the right from in front and below. She developed a slight degree of papilloedema. Operation revealed flattening and congestion of the parietal convolutions on the left side. Deep x-ray therapy was instituted and an electroencephalograph now revealed an abnormal rhythm over the affected area.

In both these cases, radiotherapy consisted of 19 treatments over 4½–5 weeks. At each treatment 250 r units were given (except on three occasions) using 200 kV and a filter of 0.5 mm of copper and 1 mm of aluminium. Five fields were used, left and right lateral, frontal and occipital, all having a focus-skin distance of 70 cm, and a vertical field with a focus-skin distance of 50 cm. The total doses given were 4,040 and 4,500 r units respectively (skin doses).

Stress is laid on the importance of air encephalography in epilepsy of late onset and where fits may be hysterical in nature.

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THE VASCULAR FACTOR IN INTRACRANIAL PRESSURE AND THE MAINTENANCE OF THE CEREBROSPINAL FLUID CIRCULATION

by J. E. A. O'Connell, *Brain*, 66, 204–228, September 1943

Accurate knowledge of the sites of production and absorption of the cerebrospinal fluid (CSF) has been forthcoming only in the last thirty years or more with the work of Dandy (1919), Weed (1914), Cushing (1926) and others, although Key and Retzius in 1870 suggested that it was absorbed by means of pacchionian granulations. It is generally agreed that the choroid plexuses are the site of origin of the fluid, but difference of opinion exists as to whether it is a secretion, as favoured by Faivre (1854) and Flexner (1934), or whether it is a simple filtrate, as suggested by Mestrezat (1912) and Fremont Smith (1927). Weed (1935) believes that absorption of the fluid into the venous sinuses depends on two factors, (i) the osmotic pressure of the plasma proteins, amounting to 250–300 mm of fluid and (ii) the small hydrostatic pressure gradient due to the fact that the CSF-pressure is usually greater than that in the venous sinuses. This is only 15–35 mm of fluid in quadrupeds.

Different workers have attributed the normal positive intracranial tension to different factors. Weed (1929) believed that it represented the balance between the processes of production and absorption, and that the elasticity of the dura was unimportant, while hydrostatic factors were important only in positions other than the horizontal. Howe (1929) thought that the normal CSF-pressure was maintained by the secretion of fluid sufficient to distend the dura moderately. Solomon (1929) stated that the pressure tended to be constant for the individual, and believed that there was a mechanism which maintained the pressure in a state of equilibrium. Suggested factors in this maintenance are the amount of blood in the head, the balance of secretion and absorption, and the elasticity of the spinal dural sac. Fremont Smith & Kubie (1929) state that the volume and pressure of the CSF are maintained by a delicately balanced osmotic and hydrostatic equilibrium between the CSF and the blood. Difference of opinion exists about the rate of formation and absorption of CSF, some workers suggesting 500–800 cm³ per 24 hours, while others suggest a very much smaller amount. Among factors responsible, apart from local formation and absorption, for the circulation of the fluid, cerebral pulsation varying with cardiac and respiratory activity has been considered, but the variations due to this pulsation are slight, and little importance is attached to them. Greenfield & Carmichael (1925), however, suggest that the replacement of fluid in the spinal canal is due to such pulsation.

The present author performed lumbar and cisternal punctures on the cadaver at varying periods after death and found that, in the horizontal position, the CSF-pressure was never greater than atmospheric. As the blood ceases to circulate, the formation and absorption of CSF also ceases at the time of death, and so a diminution in volume of CSF cannot occur. The fall of pressure which occurs after death can therefore be accounted for only by an increase in the volume of the subarachnoid space. He believes that such a change does occur and is due to diminution in size of intracranial blood vessels.

The author also recorded the variations in CSF-pressure with cardiac and respiratory activity during lumbar, cisternal and ventricular puncture, in all patients investigated over a period of 18 months. Although, at lumbar puncture, there is a wide range in normal subjects in the horizontal position, usually said to be between 80–180 mm of fluid, the variations due to cardiac and respiratory activity differ only slightly from case to case. The former may be no more than 1 mm, with often less than 0.5 mm, and the latter amounts to 2 mm or more. The same results were obtained with cisternal puncture in the horizontal position. With ventricular puncture, however, undertaken with the body horizontal but the head raised to allow simultaneous tapping of both lateral ventricles in the occipital region, the intraventricular pressure is lowered, but cardiac and respiratory activity produces much greater variation of CSF-pressure, the former lying between 5–50 mm with an average of 15 mm, and the latter varying from 15–60 mm with an average of 35 mm. Therefore intraventricular pressure is subject to recurring variations.

The author discusses the reasons for the difference in variations of pressure according to the site of puncture, and shows that it is due to a difference in diameter of tubing or needle through which the pressure variations have to be transmitted to allow of their manometric measurement. This was demonstrated experimentally on a model in which variations in hydrostatic pressure in a reservoir, of different magnitudes and rates, were conveyed to a manometer through systems of different diameter.

The widely held view that the CSF-pressure is subject to slight and unimportant variations is thus erroneous. It does in fact vary rhythmically through an average of 80 mm every 3–4 seconds. This is further substantiated by the observations frequently made during craniotomy or laminectomy, when cerebrum and overlying dura are elevated at each cardiac contraction. If a large subarachnoid channel is pricked a jet of CSF will often escape, and its height varies with cardiac and respiratory activity, in contrast to lumbar-puncture findings.

The CSF-pressure measured by lumbar puncture varies with the position of the patient. It is increased in the vertical position, and decreased by lowering the head below the lumbar region. This indicates that the subarachnoid space

is not a rigid system, but is vented, and this is generally believed to be brought about through the vascular system. Weed (1929) has shown that this venting is incomplete and that the nervous system is protected against great alteration in the CSF-pressure. When a patient is in the horizontal position for lumbar puncture, the subarachnoid space of the uppermost cerebral hemisphere is entirely above the horizontal plane, and the height of this resulting column of CSF represents the hydrostatic fraction of CSF-pressure as measured in the lumbar region. This can be calculated by halving the maximal diameter of the head after making due allowance for thickness of cranium and scalp. In a series of adults it was found to be approximately 50 mm. This was thought to represent the hydrostatic fraction of the CSF-pressure in an adult.

It has been calculated that the variation of intracranial pressure with respiratory fluctuations of the volume of intracranial venous blood averages 40 mm, and as the volume of intracranial blood increases with cardiac systole the average rise in CSF-pressure amounts to 40 mm, giving a total variation of pressure of 80 mm or more recurring every few seconds. The usual recording system will not register such rapid variation. The fluid in the manometer takes up a mean position between the two extremes, oscillating a millimeter or less on each side of this position. The vascular factor will thus add an average of 40 mm of pressure to the 50 mm hydrostatic factor. These two factors contribute approximately 90 mm to the average normal CSF-pressure of 120 mm in the horizontal position. The balance between production and absorption of the fluid must play a part in contributing to the remainder, as shown by the fact that an obstruction in the CSF-circulation causes a rise in pressure, whereas removal of CSF causes a fall. Under normal conditions, however, the author believes that this factor is more concerned with regulation of volume than with pressure of the CSF.

Fremont Smith & Kubie (1929) suggest that the mechanism of circulation of the CSF is the same as that of Starling's description of the mechanism of the circulation of tissue-fluids in general. This is that, on the arterial side of the capillary loop, vascular hydrostatic pressure is greater than smotic pressure of plasma-protein, and hence fluid filters into the tissues. The reverse is the case at the venous end of the capillary loop. The author believes that this is not an adequate explanation, but that another vascular factor plays a part. With each cardiac systole, and during the period between each inspiration, there is an increase in the volume of the intracranial blood. CSF must therefore be displaced. The volume of the cranium and brain is constant. The author believes that this displacement occurs in two directions, (a) into the spinal canal, where expansion of the dura allows its accommodation, and (b) into the area of lowest intracranial pressure, which in most normal postures, when the head is above the level of the trunk, is lowest in the region of the vertex. The mean pressure at the base of the skull is greater than at the cranial vault. The increase in volume of intracranial venous blood during expiration will mainly affect the venous sinuses at the base of the skull owing to gravity. The systolic expansion of the intracranial arteries will be largest in the basal arteries. Thus, increase in intracranial blood-volume during expiration and systole occurs largely in the basal part of the cranium, and displaces CSF towards the site of lowest intracranial pressure, i.e. the superior sagittal sinus. So, at every cardiac systole and expiration, the ventricles are compressed, fluid is expelled into the subarachnoid space, and fluid is also driven from the base to the vertex. At inspiration and diastole, reflux occurs, but this is probably not equal to the influx. According to this view, the circulation of CSF is assisted by a vascular pump.

The author believes that it is possible that the development of the arachnoidal granulations (and lateral lacunae into which they protrude), which occurs in later life, is due to the rhythmic thrust of fluid into the arachnoid villi in relation to the superior sagittal sinus. In most positions of the head when it is above the level of the trunk, the superior sagittal sinus will be relatively empty of blood, and hence the variations of rate of venous outflow from the skull, e.g. with respiration, will be reflected here later and to a less extent than in the basal sinuses. With each recurring elevation of CSF-pressure of about 80 mm, fluid will be driven through the subarachnoid space towards this region and this

rhythmic thrust of fluid into the villi in relation to the superior sagittal sinus causes the villi to enlarge.

The author also suggests that the observations provide an explanation of the localized ventricular dilatation, which may occur in relation to areas of focal brain-damage in the presence of normal or subnormal intracranial pressure. This may occur within a few hours, and it is suggested that the regularly-occurring increases in intraventricular pressure and expiration are responsible by exerting intermittent thrusts of pressure on the injured or weakened ventricular wall. A similar explanation will apply to the condition of traumatic cerebral fungus. This would thus be improved theoretically by repeated lumbar puncture, and the author found this to be efficacious in practice. The occasional development of a generalized internal hydrocephalus in the presence of normal or subnormal intracranial pressure, e.g. after closed head injuries, may be due to similar generalized cerebral damage. The bony absorption and changes in the skull which occur with a raised intracranial pressure are probably due to similar pulsatile changes in the CSF-pressure, as mere contact of tissue does not lead to bone absorption, whereas pulsatile tissues do so.

In children, closed cranial fractures may be followed by absorption of bone until the linear fracture is replaced by a wide defect through which the pulsations are transmitted to the scalp. Occasionally this progresses until the rare cephalohydrocele develops (ventricular cyst). The author explains this as follows: a fracture of the skull-vault in a child may be unassociated with a scalp wound, and yet because of the relatively unresistant skull a dural tear and severe focal cerebral damage may occur. The lateral ventricle dilates into the damaged area of cerebrum and the diverticulum projects into the dural tear. If the latter be small, the only consequence will be local bone absorption at the fracture site. If the tear is large the pulsation of the ventricular diverticulum will produce a wide area of bone absorption and a cephalohydrocele will thus form.

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SPONTANEOUS SUBARACHNOID HAEMORRHAGE A review of 150 cases

by C G Magee, *Lancet*, 2, 497-500, 23/10/43

Symonds (1923, 1924) first stimulated British interest in this subject and a large literature has now accumulated. The circle of Willis is remarkable in lying in a fluid space and depending on the hydrostatic support of the fluid. The branches come off at acute angles and it is now suggested that there is the impact of a double thrust on each communicating branch with every cardiac systole from both ends of these vessels simultaneously. A decade ago it was widely thought that the principal cause of aneurysm of the cerebral arteries was a congenital muscular defect of the media located at the acute angle of bifurcation. This region corresponds with the point of maximum pressure in the vessel walls under ordinary conditions of circulation. Degeneration of the

internal elastic lamina, due to continual overstretching, is the final stage in the production of the sac (Forbus, 1930, Schmidt, 1930, Strauss, Globus & Ginsburg, 1932) Such a muscular defect at points of bifurcation is, however, commonly found in other vessels which do not form aneurysms, and also such arterial defects are frequently found in the circle of Willis without aneurysmal formation (Fetterman & Moran, 1941) Glynn (1940) concluded that medial defects were in themselves of little importance in cerebral aneurysmal formation, but that the concentration of the elastic tissue in the internal elastic lamina in the cerebral vessels—instead of being distributed throughout media and adventitia as in other vessels—rendered the tissue more vulnerable to injury and therefore to degeneration

The present author has reviewed the data of 150 cases of spontaneous rupture of an aneurysm of the circle of Willis resulting in subarachnoid haemorrhage Most of the cases were those discharged from the Armed Forces or Civil Defence Services There was therefore selection of material with regard to age and sex However, the author concludes that the incidence is low under the age of 20 and then rises sharply It is far more common in males Furthermore the prognosis with regard to recurrence, death and functional recovery is worse with increasing age Good functional recovery is rare between 41 and 50 years of age

There was little of importance in the previous health and family history of the patients The mode of onset was carefully examined In 8 cases a comparatively minor trauma was important, such as heading a football or a simple fall Only 15 cases could be related to physical strain In 43 cases the onset occurred in bed, on rising, or in the home, office or cinema This is strong evidence against the importance of physical strain as an aetiological factor Premontory symptoms or signs included headache of long duration in 18 cases, often labelled as migrainous and associated with visual disturbance or ocular palsy When the major attack developed, notable lumbar pain preceded the main symptoms in 3 cases

The presenting symptoms and signs are shown in the accompanying table In all but one of the 16 ophthalmoplegic cases, the aneurysm lay on the anterior half of the circle or its branches Albuminuria occurred in 15 cases and glycosuria in 7 cases Haematemesis occurred 3 times Loss of consciousness and vomiting, either alone or together, were of serious import as regards survival The mortality-rate was 56% (84 deaths) The blood-pressure reading was of no prognostic value

PRESENTING SYMPTOMS, SIGNS AND OTHER FINDINGS IN 150 CASES OF SUBARACHNOID HAEMORRHAGE		
Findings	Cases	Remarks
Pyrexia	9	Usually 100–103° F [about 38–39.5° C.], (in one case 106° F)
Pulse rate		
Over 70	5	} Out of 29 observations
40–60	23	
Headache	105	14 occipital
Loss of consciousness	75	—
Neck rigidity	77	—
Convulsions	19	—
Vomiting	64	—
Vertigo	25	—
Photophobia	11	—
Diplopia	8	} Aneurysm demonstrated at necropsy in 5
Objective ophthalmoplegia	8	
Papilloedema	11	
		Noted on 1st day in 5 cases, latest case appeared on 13th day
Vascular hypertension		
Diastolic over 100 mm Hg	7	} Blood pressure recorded in 63 cases
Systolic over 150	11	
Wassermann or Kahn test	35	All negative

Of the 84 fatal cases, 58 reached necropsy and in 43 a single ruptured aneurysm was found In the others, multiple aneurysms were present They are much more common on the anterior half of the circle (27/9) and on the right than the left sides (2/1) The latter is the reverse of the common experience of intracerebral haemorrhage of other varieties

Congenital horseshoe kidney was found in one case, cystic kidneys in one, the thymus was reported as “present” in 2 cases, there was an active duodenal ulcer in 1 case, and atheroma of cerebral or other vessels was present in 2 other cases A second haemorrhage occurred in 50 of the 150 cases and, as 52 cases died in the first attack, these 50 recurrences were among the 98 survivors Another 32 cases died in the second attack The commonest time of incidence of the second attack was in the first month The same preference for side and anterior position is found as in cases fatal at the first attack Of the 150 cases, 105 were either dead or seriously crippled At periods varying between 6 months and 4 years, 22 of the survivors had been re-examined Their chief complaints were of headaches, giddiness, dizziness, and sleepiness

The author concluded that physical effort was not a factor in the majority of cases in precipitating the bleeding In fact, the haemorrhage most frequently occurs during rest Raised blood pressure is not a factor

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THE PATHOLOGICAL CHANGES IN THE BRAIN IN FATAL HYPOGLYCAEMIA

by R D Lawrence, A Meyer & S Nevin, *Quarterly Journal of Medicine*, 11, 181–201, October 1942

The lack of unanimity among recent investigators as to the nature of the brain changes and the mechanism of their production in fatal hypoglycaemia arising in the course of insulin treatment for diabetes and schizophrenia led the authors of this paper, from King's College Hospital and the Central Pathological Laboratory, London County Mental Health Service, to describe in detail their findings in six fatal cases, and to use them as a basis for reviewing the whole subject

Case 1 A woman of 30 with diabetes, who died after 17 days' unconsciousness following hypoglycaemia of less than 10 hours' duration Microscopical examination showed a diffuse and widespread disappearance of nerve-cells in the frontal, central and temporal cortex, with a secondary macroglial and microglial proliferation. Similar changes were found in the caudate nucleus and the putamen. Many residual cells showed homogenizing cell change There was also a diffuse gliosis of white matter, but no gross vascular changes were seen

Case 2 Diabetic male, aged 47, who died after 12 hours' coma preceded by relapsing hypoglycaemia with lucid intervals for 36 hours A diffuse and widespread degeneration of nerve-cells was apparent in the cerebral cortex, basal ganglia, and cerebellum Homogenizing cell change and Nissl's severe cell change were predominant. No glial proliferation nor vascular changes were seen

Case 3 Male, aged 59, with 3 years' history of severe and increasing hypoglycaemic symptoms due to an islet adenoma of the pancreas Death occurred after 4 days relapsing and deepening coma Diffuse and widespread degeneration of the nerve-cells in the brain was seen. Those which remained showed homogenizing, ischaemic, and Nissl's severe cell change The distribution was the same and again no vascular changes nor glial proliferation were apparent

Case 4 Male, aged 23, who died of hypoglycaemia during insulin treatment for schizophrenia. Microscopical examination again revealed widespread changes in nerve-cells corresponding to Nissl's severe cell change

Case 5 Male, aged 20, who died during hypoglycaemic coma of 37 hours duration from insulin treatment of schizophrenia Widespread acute swelling of nerve-cells was seen, with Nissl's severe cell change and diffuse gliosis in the cerebral and cerebellar white matter and the brain stem

Case 6 A diabetic who died after 36 hours' hypoglycaemic coma There was widespread loss of nerve-cells with severe homogenizing changes in most of the residual neurones

Discussion

The changes described closely resemble those recorded in the literature, particularly in the detailed studies of Stief & Tokay (1932 & 1935), Bodechtel (1933), Leppien & Peters (1937), Cammermeyer (1938), Ferraro & Jervis (1939) and Winkelman & Moore (1940) Similar changes have been reported in vascular and anoxic conditions, such as epilepsy, status epilepticus (Scholz, 1933), and pertussis eclampsia (Husler & Spatz, 1924) Carbon monoxide poisoning and strangulation may produce very similar changes Owing to their similarity with the changes that occur in vascular and anoxic conditions, most workers have interpreted the changes in hypoglycaemia on a vascular basis It is here suggested that removal of sugar from the brain may lead to changes similar to those produced by oxygen lack In hypoglycaemia lack of glucose is extreme As the usual estimations include 20 mg per 100 cm³ of reducing substances other than glucose, the common reading of 20 mg per 100 cm³ found in hypoglycaemia indicates a total absence of glucose in the blood As a result of this absence of the main, if not the only, substrate which the brain can use for its oxidative processes, oxygen utilization by the brain cells is suspended The authors suggest that it is hardly correct to use the term intracellular anoxia to describe the hypoglycaemic mechanism, as this term is reserved for the failure of the tissues to receive an adequate supply of oxygen and not for the absence of an oxydizable substrate In their opinion the new word *oxyachrestia* would be a useful and accurate description

It is probable that vasomotor disturbances also arise These tend to aggravate the non-utilization of oxygen, and may be held largely responsible for the gross haemorrhages which have been reported in the literature Epileptic convulsions, although common in severe hypoglycaemia, are insufficient to cause these brain changes, which may also occur in their absence Some aggravation is, however, possible

Conclusions

- (i) Similar changes occurred in the brain in 6 fatal cases of hypoglycaemia These were widespread degeneration and necrosis of nerve-cells, with macroglial and microglial proliferation, and homogenizing and severe cell changes The cerebral cortex and basal ganglia were affected most, the cerebellum less so, and the lesions in the remaining centres of the brain-stem were slight
- (ii) The main cause is considered to be the failure of the vital oxidative processes from the lack of the substrate glucose, possibly reinforced by subsequent vasomotor changes

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THE AFTER-HISTORY OF 1,075 CASES OF CEREBRO-SPINAL (MENINGOCOCCAL) MENINGITIS IN LONDON AND ENVIRONS

by E C E Maddock, *Monthly Bulletin of the Ministry of Health and the Emergency Public Health Laboratory Service*, 2, 111-115, November 1943

The success obtained with sulphonamides in the treatment of the acute stages of cerebrospinal meningitis is well known It seemed desirable to ascertain the after-histories of patients so treated The author followed up 1,075 such cases in which the diagnosis had been proved bacteriologically The time-interval between discharge from hospital and the report on the condition by letter or health visitor ranged from 1 to

24 months Of the 1,075 cases, 254 (23.6%) complained of some disability arising during or since the illness The following table was compiled

AGE AND SEX-DISTRIBUTION OF PATIENTS VISITED AND THE NUMBER IN EACH AGE-GROUP IN WHICH SEQUELAE WERE FOUND

Age in Years	Total number visited			Number with sequelae			Percentage incidence in each age-group
	Total No	Male	Female	Total No	Male	Female	
Under 1	62	35	27	7	2	5	11.3
1-3	132	74	58	14	8	6	10.6
3-5	94	49	45	15	7	8	16.0
5-15	170	83	87	35	22	13	20.6
15-25	248	146	102	61	38	23	24.6
25-45	229	139	90	71	38	33	31.0
45-65	122	45	77	42	18	24	34.4
65 +	18	9	9	9	6	3	50.0
Totals	1,075	580	495	254	139	115	—
Percentage	100	54	46	100	54.7	45.3	23.6

Percentage incidence of sequelae according to sex
Males = 23.9 Females = 23.2

The disabilities were listed in the following terms, with numbers attached

Deafness, total	13	Weakness of legs	22
Deafness, one ear	11	Nervous	19
Deafness, partial	13	Irritability	30
Blindness, total	1	Changed disposition	18
Blindness, one eye	6	Depressed	18
Error of refraction	35	Poor memory	12
Lachrymation	4	Lack of concentration	7
Strabismus	10	Pain	28
Headache	117	Weak and easily tired	27
Hydrocephalus	1	Arthritis	6
Spastic paralysis	1	Retarded or poor development	9
Abscess of spine	1	Nystagmus	1
Mastoid abscess	1		
Facial paralysis	1		

There was no obvious relationship between the kind of employment and sequelae except that their incidence in school-children was low The figures given for ocular complaints should be treated with reserve In some patients, complaining of weak sight after their illness, correction of refractive errors by spectacles relieved the symptoms The incidence of ocular sequelae differs greatly Heath (1937) quotes the incidence as varying between 9.3% and 65.3% The after-effects on the central nervous system are difficult to gauge in regard to intensity and permanency Fifty-two (6.5%) of the patients with no sequelae suffered from severe headache and completely recovered, the headache gradually diminishing Twenty-eight patients complained of muscular pain in different parts of the body

The relationship between the incidence of sequelae and the day of disease on which treatment was commenced was investigated in 419 patients (98 complained of sequelae), and it was shown that the percentage of cases without sequelae was higher in those treated on the day of onset than that of cases in general No marked difference was observed when treatment was begun on later days No satisfactory conclusion can be drawn from the relation of dosage of sulphonamide and incidence of sequelae

Spontaneous recovery from sequelae was relatively frequent Medical sampling of 221 cases was undertaken, 51 were reported to be suffering from sequelae and 31 of these were examined 3 to 8 months after interview by the health visitors Their ages ranged from 1 to 62 years, with equal sex-distribution It appeared from the medical examination that rather less than 1/3 of the sequelae mentioned in the nurses' report were confirmed At least 1/3 of the 23.6% sequelae suggested by the nurses could reasonably be regarded as transient,

giving a final figure of 7-8 %, who suffer from after-effects of meningitis from 9 months to 2½ years after their discharge. Deafness is by far the largest cause of disability. In most series it ranges from 2 % to 3 % and rarely as much as 5 %.

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VITAL STAINING IN BRAIN SURGERY A preliminary note

by A. Sorsby, A. D. Wright & A. Elkeles, *Proceedings of the Royal Society of Medicine*, 36, 137-140, January 1943

In 1937 Sorsby, Elkeles, Goodhart & Morris reported the successful staining of retinal lesions in the living experimental rabbit by a non-toxic dye, *Kiton Fast Green V*. The significance of this work was (i) that it was possible to obtain vital staining in nervous tissue, and (ii) that this procedure opened the possibility of making visible in life such translucent tissues as damaged retina. These workers failed to obtain any staining of the normal retina, and the brains of rabbits showed staining of only the grey matter, the white matter remaining unstained. The clinical applications of vital staining in ophthalmology have been recorded by Sorsby in a series of papers in 1938, 1939 and 1940, and the authors of the present paper report an investigation of the possibilities of vital staining in the course of intracranial operations.

The principle underlying the use of *Kiton Fast Green V* in brain operations is that the dye can be used as a contrast staining agent in life, for not only is there a differential staining of grey and white matter in the normal brain, but also a differential staining in different pathological states. The dye was injected intravenously as 30-50 cm³ of a 10% solution. Contrast staining was not obtained in a patient with a metastatic deposit situated in the occipital lobe and originating from a renal carcinoma, nevertheless, the margins of the tumour, which itself remained unstained, were intensely green. A negative result was obtained with angioma. The most striking appearances were seen in a patient diagnosed as suffering from glioma, the tumour stood out intensely green against the unstained brain tissue. (With the doses used clinically the grey matter does not show any staining.) Actually this tumour proved to be an unusual type of granuloma, and in a case of verified and recurrent glioma no staining was seen except when the tumour was cut with the diathermy loop, when the cut surface showed a vivid green.

The authors point out that this work is still in an experimental stage. The dye has not yet been biologically standardised and the dosage is still uncertain, although it appears to be without ill effects in the doses so far used. It is suggested that the vital-staining technique described might often be of value in a difficult surgical situation. For example, the treatment of ill-defined tumours and of traumatic epilepsy by excision of cicatrices of the brain might be greatly facilitated.

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Psychological Studies¹

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THE OBJECTIVE STUDY OF MENTAL IMAGERY I. PHYSIOLOGICAL CONCOMITANTS With appendix on a new method of electroencephalographic analysis

by F. Golla, E. L. Hutton & W. G. Walter, *Journal of Mental Science*, 89, 216-223, April 1943

The respiratory movements of some 60 patients were recorded as well as the cortical potentials (by means of the electroencephalogram) while they were performing a variety of tasks calling for different modes of imagery. It was found

¹ [See also *BMB* 636, 642, 643, 644 —ED.]

that persons with only sensory imagery, either visual or auditory, were regular breathers, while those whose imagery had a kinaesthetic component, were irregular. A number of different test problems was given to the subjects, but the most consistent results were obtained by giving a series of multiplication sums of increasing difficulty. The patients were classified according to whether the alpha rhythm in the electroencephalogram was extremely small (the M group), or of average size and present to an equal extent at all times (P group), a third group (R group) were those in whom a clearly visible rhythm of the usual size was present when the eyes were shut, and was blocked or diminished by opening the eyes or by vigorous mental exertion.

The results of this preliminary study suggested that in the P group were to be found those whose preoccupation with verbal and kinaesthetic imagery was such that when they opened their eyes this did not in itself provide an adequate stimulus to the mechanism for integrating visual imagery and perception, whereas in the M group this mechanism continued to operate when their eyes were shut because of the use of visual imagery by the subjects. The P group showed predominantly the irregular respiration often associated with auditory kinaesthetic imagery, and the M group the regular respiration characteristic of visual imagery.

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SUGGESTIBILITY AND HYSTERIA

by H. J. Eysenck, *Journal of Neurology and Psychiatry*, 6, 22-31, January-April 1943

The view that hysteria is associated with increased suggestibility has been held for many years. Janet (1907) maintained that the most important mental stigma of hysteria is suggestibility. Similar views were expressed by Babinski & Froment (1918), McDougall (1911), and many other psychiatrists. As experimental evidence in support of these views was almost entirely lacking, Dr Eysenck submitted the question to investigation.

Using 8 tests of suggestibility on groups of hysteric and non-hysteric patients of both sexes, he found that in none of the tests of suggestibility were there significant differences between hysterics and non-hysterics. Neither was there any significant sex-difference in suggestibility. Analysis of the correlations between the various suggestibility-tests revealed the existence of two types of suggestibility, referred to as primary and secondary. Primary suggestibility was distributed in the experimental population in the form of a U curve, and had a significant non-linear correlation with intelligence, indicating that persons of average intelligence showed higher primary suggestibility than the highly-intelligent or dull.

Secondary suggestibility was found to be normally distributed and correlated in a linear manner with intelligence, the more intelligent tending to show less secondary suggestibility. Further differences in these two types of suggestibility are that tests of primary suggestibility show high re-test reliability and that primary suggestibility is related to hypnosis, whereas secondary suggestibility has a low re-test reliability and is not related to hypnosis.

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NEUROSIS AND INTELLIGENCE

by H. J. Eysenck, *Lancet*, 2, 362-363, 18/9/43

Hollingsworth (1920, 1931) found in several hundred military cases that, except for the psychasthenic group, all types of neurosis fell definitely below the intelligence-level of the average recruit. Similar results were found by Tendler (1923). The results of Michaels & Shilling (1936), however, did not support the hypothesis that neurotics are on the average less intelligent than normal people.

In view of these conflicting results, Dr Eysenck reports the findings of the progressive matrices intelligence test on 3,000 neurotic men and women admitted to Mill Hill Emergency Hospital, where the test is given to all admissions.

This is a perceptual test of intelligence, which divides subjects into five grades containing respectively 5 %, 20 %, 50 %, 20 % and 5 % of the total population (Raven, 1941, 1942). The most intelligent 5 % of the population are in grade I, and the least intelligent 5 % in grade V.

In this series the men were, in general, very slightly below average, while the women were even more slightly above average. The slightly lower values in the men were probably due to selection rather than to any connection between neurosis and low intelligence. The hospital deals only with military personnel below commissioned rank, and does not, therefore, cover a true sample of the whole population.

The author's results are in opposition to those of Hollingworth (1920) and Tendler (1923). One way in which a reconciliation might be effected is suggested by Babcock (1941) who found that "the lower intelligence of neurotics is caused by weakness in the efficiency phase of mental organization rather than ability to abstract and reason".

The author states that it is possible to argue that the tests used by Hollingworth and Tendler were of "efficiency", while the test used in the investigation was of level of intelligence. He concludes that neurotics do not, on the average, differ from normal people in their intellectual level: any intellectual inferiority that may be found is due to a weakness in their "efficiency of mental functioning".

It was found that, both among men and women, conversion hysterics were on the average distinctly less intelligent than other neurotics, while dysmnestic hysterics were, in general, of average or slightly above average intelligence. Patients suffering from chronic anxiety were on the average more intelligent than other neurotics. This was true of both men and women.

The frequency-distribution curve of intelligence-scores in the neurotic groups is distinctly abnormal. The curve is markedly platykurtic in the neurotic group as compared with the mesokurtic curve found with normal subjects. In other words, among neurotics tested there were far less cases of average intelligence (grade III) than one would have expected, and far more cases of either high or low intelligence.

As far as they go, the results disprove the belief that neurosis is directly correlated with low intelligence, and rather support the view that it is people of above and below average intelligence who tend to become maladjusted to their environment and develop a neurosis. The average person is less likely to become maladjusted.

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TYPES OF PERSONALITY A factorial study of seven hundred neurotics

by H. J. Eysenck, *Journal of Mental Science*, 90, 851-861, October 1944.

In order to determine the fundamental trait vectors in terms of which personality and temperament can be most economically described, Dr. Eysenck carried out a factor-analysis on the intercorrelations of 39 psychiatric traits in a group of 700 neurotic soldiers successively admitted to Mill Hill Hospital.

The first factor extracted had positive saturations throughout and contributed 14% to the variance. This factor is defined by the items having the highest saturations with it, i.e. badly-organized personality, dependent, abnormal before illness, discharged from the Army, narrow interests, little energy, much unemployment, dyspepsia, schizoid personality, and unsatisfactory home, to name only those with relatively high saturations. This factor is therefore one of "neuroticism" or "lack of personality integration", it is almost completely defined by the item "badly organized personality" which correlates with the factor to the extent of 0.92.

The second factor is bipolar and presents us with a dichotomy which contrasts on the one hand anxiety, depression,

obsession, apathy, irritability and on the other hysterical conversion-symptoms, narrow interests, little energy, sex anomalies, hysterical attitude, no group-membership and lack of vocational skill. This differentiation supports Jung's (1930) division of functional nervous disorders into hysterical (extraversion type) and psychasthenic (introversion type). Similarly, McDougall (1926) divided neurosis into the dissociative or hysteria class associated with an extraverted temperament, and a neurasthenic class associated with an introverted temperament. Instead of the obsolescent terms psychasthenia and neurasthenia, Dr. Eysenck suggests the term affective disorder or "dysthymia" for the anxiety depression-obsessional group of symptoms.

The third factor is characterized by hypochondriasis, effort-intolerance, dyspepsia, fainting fits, pain, hypochondriacal personality, somatic anxiety, etc. This factor is labelled "hypochondriasis".

The fourth factor was found to be of little general interest and divided the men examined into a social-misfit group on the one hand, and a psychological-conflict group on the other.

The first factor seems to be related to such concepts as McDougall's (1908) "self-regarding sentiment", Freud's (1929) "ego ideal", Janet's (1924) "psychic tension" and Pavlov's (1941) "strength of nervous functioning".

The second factor in addition to being in line with the theoretical views of Jung and McDougall agrees with more recent typologies, e.g., Eppinger's (1917) vagotonic and sympatheticotonic types, Kempf's (1941) anabolic and catabolic types, Kretschmer's (1936) schizothymic and cyclothymic types and Jaensch's (1930) B- and T-types (to mention only a few).

Dr. Eysenck also quotes results obtained from questionnaires, ratings, and experimental and animal studies, which are also in agreement with the findings of the factorial analysis. Thus there appear to be two predominant modes of personality organization.

(i) Strength of nervous functioning, psychic tension, self-regarding sentiment, super ego or, as this factor is called, integration as opposed to disintegration or neuroticism.

(ii) Affective disorder, desurgency introversion, repression or, as this factor is called, dysthymia as opposed to hysteria.

Work is in progress to determine the most discriminative objective tests of these two main factors.

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AMNESIA IN ALTERED STATES OF CONSCIOUSNESS

by A. Paterson, *Proceedings of the Royal Society of Medicine*, 36, 573-576, September 1943.

Fully-conscious behaviour requires adjustment not only to the immediately perceived setting and what has preceded it, but also to a wider background of past experience. Without this continuity of experience, which memory provides, behaviour would lack continuity, and episodes isolated from the general experience may take place, and usually cannot be recalled. The carrying out of an act under hypnotic suggestion has no continuity with past or future experience of the patient, and cannot be recalled in normal consciousness, as a similar setting or orientation would be needed for its recall.

Dr. Paterson reports case-histories of patients with head injury who, after recovery of normal consciousness, had episodes of isolated behaviour with subsequent amnesia, which are closely analogous to the dissociated behaviour under hypnosis. He points out that similar phenomena occur in epilepsy and emotional stress, and quotes interesting

illustrative examples Though differing in aetiology there are important points of similarity in that they show the same cognitive and emotional isolation of the reaction and the same proneness to later amnesia

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CLINICAL TESTS OF MEMORY IMPAIRMENT

by O L. Zangwill, *Proceedings of the Royal Society of Medicine* 36, 576-580, September 1943

Mr Zangwill, in an interim report, describes some simple tests developed at the Brain Injuries Centre in Edinburgh for assessing memory-defect Three simple learning-tests are described, two are verbal and the other a performance test The first verbal test is the digits-test which forms part of the Bellevue Intelligence Scale (Wechsler, 1939) First memory-span is ascertained, and then the minimal number of repetitions needed to obtain correct recitation of digits exceeding the span In organic retention-defect, disparity is found between the memory-span for digits and the number of repetitions needed for correct reproduction of longer sequences

The second verbal test is adapted from Babcock's sentence-repetition test (Babcock, 1930) The sentence "One thing a nation must have to become rich and great is a large secure supply of wood," is repeated alternately by examiner and patient until the latter gives two consecutive word-perfect versions If more than 8 consecutive repetitions are needed for correct recitation in non-psychotic patients above defective level of intelligence, some retention-defect is indicated

The author points out that, although longer paragraphs may be necessary for testing highly intelligent individuals, the test is satisfactory for the majority of patients

The third test is the Rey-Davis performance-test, consisting of four boards, in each of which are nine pegs eight being movable and one fixed The patient finds the fixed peg by trial and error and the test is repeated in the same order until the patient can demonstrate unhesitatingly the position of the fixed peg on all 4 boards The test can be prolonged by rotating the boards through various angles

In organic retention-defect, learning is slow and may differ qualitatively from the normal performance in one of the following ways stereotyping of errors, confusion of sequence, instability of learning, forgetfulness, and breakdown on rotation

Two varieties of memory-impairment were revealed by these tests (i) organic reaction-type characterized by impairment of learning, (ii) neurotic pattern characterized by exaggerated variability of response with notable tendency to fail on easy tests

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Psychoneurosis in Wartime¹

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DISCUSSION ON FUNCTIONAL NERVOUS STATES IN RELATION TO SERVICE IN THE ARMED FORCES

by Lord Horder, D Curran, J R. Rees, R D Gillespie, W M Fairlie & H B Craigie, *Proceedings of the Royal Society of Medicine*, 36, 253-260, March 1943

Lord Horder, opening the discussion from the point of view of the military recruiting boards, pointed out that it was not the concern of these boards to post men to appropriate jobs in the Armed Forces, and that the material presenting itself was [in November 1942] more heterogeneous than in the days of voluntary enlistment. The adoption of a policy of sending all recruits to general service corps and to primary training centres for examination and posting had been a considerable advance The soldier should be given a good trial of his capacity for adjustment to the new requirements made upon him on his entry into the Service Men with mental ages of 6 or 7 were doing useful work in specially organised sections of the Army Care must be exercised in the utilization of psychological tests, which could not provide the answers to

the question whether the man's personality was appropriate to the tasks he must undertake

Surgeon Captain Curran pointed out that the Navy had been subjected to more prolonged and severe stress than the Army or the R A F (with the exception of its flying personnel) but that, on the other hand, the increased incidence of neurosis which might have been expected because of this had probably been more than counter-balanced by the high quality of the men who had joined the Navy before the war or subsequently, either as volunteers or after expressing a preference for this Service The principles on which the psychiatric organization had been based were first, that neurology and psychiatry should be regarded as two aspects of one subject closely linked with general medicine, and therefore located as far as possible as an integral part of the main naval hospitals, secondly, that early treatment is necessary—if possible, it should be without admission to hospital, thirdly, that the advantages of illness must be reduced to a minimum, e.g. by setting up a special rehabilitation unit, and finally, selection at the time of entry

Experience of the Navy suggested that 10% to 15% of the beds of a large hospital should be set aside for neuropsychiatric cases Gross conversion-hysteria had been uncommon, as it was in the Navy during the last war States of anxiety and depression, combined in various proportions, were found in the majority of the patients, frequently complicated or prolonged by hysterical mechanisms Poor intelligence, as judged by tests, had been found compatible with apparent efficiency in such branches as ordinary seamen or stokers Effort-syndrome had been rare, but tended to increase in certain groups It had been possible to keep on duty as many as 90% of new cases seen at one representative depot, the remainder went into hospital or were invalided Of those admitted to hospital, about three-quarters went back to some form of duty, and their average duration of stay in hospital was 3 weeks In order to select men who, on entering the Navy, needed further psychiatric scrutiny, carefully chosen and trained members of the Women's Royal Naval Service, supervised by psychiatric social workers, ascertained data from the recruit which could be used for deciding which men required further individual examination Only a small proportion of the men entering the Navy were found to require such examination.

Brigadier Rees reported that mild neurotic tendencies had not been found to be a bar to service and that many with definite neuroses behaved well, many eccentrics also behaved excellently The following men must be regarded as poor risks, those of low intelligence, with a bad medical and occupational record suggesting instability, those who had had frequent "gastric" and "rheumatic" symptoms, effort-syndrome, breakdown without obvious cause, short-phase cyclothymia, over-scrupulous self-drive without insight or humour, paranoid psychopathic personality, or shiftless overdependence with bad work record

Group Captain (now Air Commodore) Gillespie quoted some statistics from the R.A.F. out of 251 flying personnel who broke down, 150 had predisposition of at least a moderate degree, out of 256 ground personnel who developed neurotic illness, 222 showed considerable or severe predisposition It must not be assumed that psychotherapy was of no use for these cases "War" neurosis in general must be distinguished from "battle" neurosis, for the latter a superficial type of psychotherapy gave moderately satisfactory results, but predisposition had to be taken into account. Those in whom predisposition was most pronounced did not do so well. Methods for detecting predisposition in advance would avoid wastage in training So far as intelligence was concerned no man should be rejected on a group intelligence test alone The psychiatrist might have to decide whether the recruit was stable—the most important requirement. For the assessment of impairment, the psychiatric type of history must provide the foundation, though it would be supplemented by projection tests Gillespie set forth the arguments in favour of psychiatric and psychological selection for service in general in the Armed Forces and for combatant or technical duties and for commissioned rank

Major Craigie mentioned that a strikingly large percentage of the total number of psychiatric cases arising in the Middle East Force had shown evidence of severe psychopathic traits in their previous history In more than 20% there was a history of serious nervous breakdowns in civil life, and many of the patients had previously been in a colony for mental

¹ [See also BMB 654, 655, 656, 675, 676 —Ed.]

defectives or in a mental hospital. The policy adopted in the Middle East Forces had been to avoid as far as possible the evacuation of psychiatric cases and to retain the men on some form of duty. It would have been better if men with recognizable predisposition to neurotic breakdown had not been drafted overseas or even not retained in the Army at all.

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THE NEUROTIC CONSTITUTION. A statistical study of two thousand neurotic soldiers

by E Slater, *Journal of Neurology and Psychiatry*, 6, 1-16 January-April 1943

The author reports observations made on a group of 2,000 neurotic soldiers admitted to Sutton Emergency Hospital between November 1939 and June 1941. The cases were classified into organic states, head injury, epilepsy, schizophrenia, endogenous depression, mental defect, psychopathic personality, anxiety-neurosis, hysteria and reactive depression. There were also small groups of obsessional neurotics, enuretics and malingerers which were too small to be dealt with severally.

The various diagnostic groups showed no significant differences in respect of age or religion. With regard to occupation it was found, as expected, that mental defectives came preponderantly from unskilled labourers, and schizophrenics mainly from sedentary occupations. Psychopaths were rarely found to be skilled workmen, perhaps because a psychopathic personality would be a hindrance in completing an apprenticeship.

The frequency of non-commissioned officers was highest in obsessionals, manic-depressives and reactive depressives. Body-build was classified (by inspection only) into asthenic, athletic and pyknic types. It was found that endogenous depressions were associated with pyknic habitus and mental defect with asthenic habitus.

Inhibited sex-life was especially frequent among mental defectives and psychopaths, and especially infrequent in cases of head injury. In 55.7% of the cases there was positive family history of neurosis, psychosis, psychopathy or epilepsy. The highest incidence of a positive family history was found in psychopathic personality (72.5%). Some degree of childhood neurosis was found in 58.8%, the frequency of definite neurosis being significantly high for psychopaths and significantly low for organic cases and manic-depressives. It seemed clear that neurotic symptoms in childhood, especially if they reach a severe degree, are of considerable significance for later life.

Almost a quarter of all patients, and over two-thirds of endogenous depressives, had had previous nervous breakdowns. Abnormal personality occurred in 40% of cases. The most common abnormal traits of character were, undue lability of mood, lack of interest in and talent for mixing socially, anergia and weakness of character, and tendencies to anxiety. Hypochondriacal and paranoid traits were the least frequent.

About a third of the patients were of poor intelligence, and the frequency-distribution curve differed from the normal in being markedly skewed, indicating that persons of low intelligence were represented in far greater numbers than those of superior intelligence.

A bad home-environment in the form of excessive poverty, drunkenness or family disagreement was found in 20.9%. The author points out that, although a bad home-environment may certainly predispose to neurosis, the finding is entirely ambiguous, as it is probably also an expression of neurosis or psychopathy in the parents and thereby a function of bad heredity.

Depression, anxiety, and hypochondriasis were the commonest symptoms and were found with considerable frequency in all diagnostic groups, and therefore seem to have a non-specific character, although they are relatively less frequent in organic and endogenous states. Hysterical symptoms, which were next in order of frequency, were very rarely found in schizophrenics. Obsessional symptoms were comparatively rare, and the only groups tending to show them with any frequency are the schizophrenics, psychopaths and reactive depressives.

Statistical figures reflect the uniformity but not the fluidity of the symptomatology of the neurosis. During their hospital stay, patients tended to lose the affective features

of their illness, and in their place hysterical aspects of the personality appeared for the first time. Symptoms were found to be of secondary importance, and are of significance for prognosis and ultimate disposal only in so far as they are indications of something more fundamental.

Patients with organic syndromes had less in the way of neurotic traits of personality, and correspondingly less in neurotic symptomatology. The same applies, but to a less extent, to epileptics, mental defectives, the schizophrenics and the endogenous depressives.

The mental defectives showed an increased liability to hysteria. The schizophrenics tended to have abnormal personalities with marked tendencies towards paranoid and unsociable attitudes, but on the other hand they showed an absence of hysterical traits of personality and of neurotic symptomatology when ill. Relative freedom from constitutional hysterical tendencies also distinguished the anxiety neurotics, in whom there was a high incidence of illness of definite exogenic precipitation and of short duration.

The following items were associated with a better-than-average chance of return to duty: Nonconformity of religious confession, non-commissioned military rank, normal childhood history, good school-record, previous army service, satisfactory home life, breakdown occurring under military stress or with other adequate precipitation or with head injury, short duration of illness, and treatment by psychotherapy. The opposite was true of asthenic habitus, positive family history, neurosis in childhood, certain abnormal personality traits, poor intelligence, unsatisfactory home circumstances and duration of illness exceeding 2 years. In general the factors which seem to be associated with eventual disposal are constitutional. Neurotic childhood, obsessional symptoms, and abnormal personality, are of particularly bad omen.

The favourable and unfavourable features were very similar to those noted as of prognostic significance in the follow-up study of soldiers returned to duty carried out by Lewis & Slater (1942). Military stress had a special tendency to produce anxiety-symptoms, hysteria, and particularly amnesia. Analysis of the findings indicated that of all neurotic symptoms, obsessional symptoms are most firmly-rooted on a basis of specific predisposition, the next in order being hysterical and paranoid symptomatology.

Hypochondriacal, depressive, and anxiety symptoms seem to be of all neurotic symptoms those most directly related to exogenic factors. The finding agrees with our preconceptions, under certain circumstances it would be abnormal not to be afraid or depressed, or somewhat preoccupied with bodily processes.

The hypothesis presented is that neurosis represents a special case of a generalized type of behaviour and signifies a failure of adaptation. The two primary reagents are the individual constitution and the environmental set-up of the moment. The individual constitution is in greater part determined by hereditary factors, to a lesser degree by environmental circumstances of the past, producing their effects by organic lesion and by psychological and physiological conditioning. These factors, especially the first, determine the form and severity of the groups of symptoms which are the so-called neurotic states or neurosis. The momentary environment determines the time of manifestation, and to a lesser extent the severity and form, of the symptoms (e.g., the association of military stress and anxiety). Other factors, such as physical illness or physiological upset and intellectual incapacity, can have an adjuvant effect and may also influence the form of the reaction (e.g., mental defect favouring hysterical manifestation, physical illness favouring hypochondriasis). Neurotic constitution and inadequate intellectual endowment are held to be the two most important predisposing factors for the manifestation of neurotic breakdown.

Factor analysis showed that the best indicators of neurotic constitution are, in order: clinically abnormal personality, neurosis in childhood, positive family history, and poor work-record. Poor work-record is a good test of both neurotic constitution and inadequate intellectual endowment, and should have considerable attention paid to it clinically. The neurotic constitution is, then, a useful hypothesis and one which ranks with inadequate intelligence, in accounting for social insufficiency, breakdown, and impairment of efficiency for military duties.

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SOCIAL EFFECTS OF NEUROSIS

by A Lewis, *Lancet*, 1, 167-170, 6/2/43

This paper, by the Clinical Director and Lecturer in Psychiatry to the Maudsley Hospital, records the results of an inquiry into the subsequent history of neurotic soldiers discharged from the Army, undertaken with a view to ascertaining whether such men are as healthy and of as much use in the civilian community as they were before joining the Army. A series of 120 soldiers, thus discharged, were investigated by personal visits to their homes in London. The average interval since their discharge into civilian life was 6½ months.

Their pre service occupations had been Professional and managerial 8, clerical and sales 20, domestic and personal service 13, Regular Army 5, skilled 17, semi-skilled 37, unskilled 20. At the time of the inquiry their occupations were Professional and managerial 4, clerical and sales 19, domestic and personal service 14, civil defence service 7, skilled 14, semi-skilled 25, unskilled 22, 15 were unemployed.

Of the 15 unemployed, 11 had done no work at all since leaving hospital. The total duration of unemployment for the whole group (273 months) was a third of the total period since their discharge (801 months). Part of this was accounted for by the period of 1 month on pay allowed to men of this category after leaving hospital. Twenty-two per cent. of the men were responsible for 55 % of the total duration of unemployment of the whole group. Only 33 men started work during the 4 weeks they were on military pay after discharge, and 24 had not obtained any work within the first 3 months.

In spite of the general rise in wage-rates and earnings, 53 of the 105 men in employment at the time of the inquiry were earning less than they did before enlistment, and 44 were doing only very light or part-time work.

Thirty-nine patients appeared to be socially unsatisfactory otherwise than in their occupations, committing minor offences such as begging or stealing or evincing outbursts of temper or constant irritability, while 58 were considered by their relatives to be in as good health as before enlistment. Sixty-three men had attended a general practitioner since discharge, and 15 had been to a hospital.

In response to 95 inquiries by letter to another group of men, whose homes were in the provinces or in Wales, 67 answers were received. Four wrote that they were unemployed and 12 that their work did not satisfy them. Of the 51 who were working, 15 reported that their health was not good, and 8 that they were in better health than ever.

A postal enquiry on the same lines, sent to the labour exchanges of the districts to which 97 ex-soldiers with homes elsewhere than in London had returned, elicited 66 replies showing that 59 of the men were at work.

The number of men who returned to the same kind of work under the same employer is high in all 3 groups (39 of the 120 Londoners, 25 of the 67 in the provinces who replied to a personal letter, and 31 of the 66 on whom the labour exchange reported).

Comparison of the findings at different periods between March 1941 and June 1942 shows that the proportion of these men who could be classed as socially satisfactory since discharge had risen. In August 1941, when inquiries about 60 of the 120 men had been made, 22 % were unemployed, and only 35 % could be classed as socially satisfactory in respect of work and otherwise, by June 1942, when the whole 120 had been visited, the corresponding figures were 12 % and 50 %. Such percentages cannot be used for exact comparison because of the somewhat arbitrary nature of any judgment as to whether a man is socially satisfactory, but they show a decided trend, here attributed to the increasing demand for labour, and to the introduction of an official scheme of rehabilitation in which the doctor and the employment exchange can co-operate in all cases.

THE SPECIAL TRANSFER SCHEME AN EXPERIMENT IN MILITARY PSYCHIATRIC VOCATIONAL RE-EMPLOYMENT

by E. D Wittkower & L. Lebeaux, *Medical Press and Circular*, 209, 366-368, 9/6/43

At the outbreak of war, when a large Army had to be formed as quickly as possible, it was soon realized that some men

were unsuited temperamentally, intellectually and physically to the jobs assigned to them in the Army, and that they consequently broke down with neurotic illness. A procedure was therefore introduced whereby men could be transferred, on the advice of a hospital psychiatrist, from one job to another, or from one corps to another, where they would do work fitted to their capacity. In the small group of 50 soldiers here reported, 11 had had superior occupations in civilian life, 26 had been skilled tradesmen, and 13 had had unskilled jobs. Twelve of the men had had less than 12 months' Army service, and 12 others were regular soldiers who had broken down as a result of terrifying experiences in the present war and failure to adjust to the increased tempo of modern training. Eighteen of the men received systematic psychological treatment before transfer. The transfer aimed at retention of these men in the Army in a non-combatant capacity, e.g. storemen, clerks, cooks, batmen, instructors, etc., thus releasing men with combatant qualities for combatant service.

REHABILITATION OF THE NEUROTIC

by L. Minski, *Journal of Mental Science*, 89, 390-394, July-October 1943

The rehabilitation of the neurotic is discussed both from the war-time and the post-war points of view. The war-time problem presents itself in two forms: (i) the military patient who returns to military duties, (ii) the military patient who is invalided from the service and returns to civil life. The value of the annexure scheme¹ in posting men to more suitable employment is pointed out.

Five hundred patients discharged to civil life were followed up, and 373 were found to be working at the end of 1 year. The author considers that many are employed only because of the present labour-shortage. He considers that careful personnel selection in industry would not only decrease the amount of neurosis but also make for more efficient work.

Industrial patients with "exhaustion neurosis" responded to modified insulin treatment and diversional occupational therapy. A large proportion of neurotic illnesses are chronic in nature and many of these patients are unable to work at all and belong to the social problems group of the chronically unemployed.

For those neurotics who could not be adequately placed, after treatment and training, in jobs in the outside world, the author suggests the establishment of colonies for neurotics after the model of Papworth Village Settlement for the tuberculous.

VOCATIONAL ASPECTS OF NEUROSIS IN SOLDIERS

by A. J. Lewis & K. Goodyear, *Lancet*, 2, 105-109, 22/7/44

Neurotic symptoms and the ability to do good work sometimes go together, but the neurotic illnesses which occur in some uprooted men and women in the Armed Forces are seldom compatible with good military work. The work may at first have been poorly done because it was uncongenial, unsuited to the soldier's capacities and previous training, not of his own choosing, monotonous, or onerous, and neurotic illness may have sprung from this failure in occupational adjustment, to which a man's neurosis will then further contribute. Or a man's military employment may be well-enough suited to his abilities and normal interests, but extraneous causes may lead to a neurotic illness which interferes with his work. Some causes and some results of neurotic illness have, no doubt, little to do with a man's work.

Even when every aspect, including the constitutional, has been given its proper emphasis and perspective in the picture of military neurosis, it is found that unfitness of the man for his present job, or of the job for the man, is frequently and impressively in the foreground.

This had become so clear by February 1941, that an array of instances and some statistics could be put before the Director of Organization of the War Office, who then instituted a procedure for altering the military employment of suitable soldiers with neurotic illness. This procedure usually referred to as the annexure scheme, allowed the hospital psychiatrist effectively to recommend suitable

¹ [see BMB 664]

placement in a military occupation for patients who would otherwise have to be discharged from the Army

Dr Lewis and Miss Goodyear describe the results of the use of the scheme at Mill Hill Emergency Hospital, where more than 1,500 soldiers and 170 women of the A T S had been dealt with by the annexure scheme by December 1943

The results of the annexure procedure have been more satisfying than those obtained before it was instituted, or without its aid since. Of those who were returned to duty during the 12 months before the introduction of the scheme, 23 % were doing full duty satisfactorily 12 months later. The corresponding figure for the year following the introduction of the annexure procedure was 46 %. As only those men who would otherwise have been discharged from the Army were dealt with by annexure, it evidently saved men for military service who would otherwise have been lost. During the 6 months before the annexure scheme, 36 % of all admissions to the hospital were returned to military duty. During the ensuing 12 months in which the annexure scheme was available, 58 % of all admissions were returned to military duty. During the five successive six-monthly periods following the institution of the scheme, the percentages of admissions (i) dealt with by annexure were 38, 41, 23, 30, 17, (ii) discharged as unfit were 41, 42, 60, 50, 54 for the same periods. The remainder of patients admitted were (iii) returned to their former units without annexure.

It is evident that an opportunity for the psychiatrist effectively to recommend suitable placement in a military occupation has good results. The psychiatrist makes the main recommendation, but he may take into account considerations other than medical in the narrower sense, in forming his judgment about suitable vocational placement.

The authors investigated the possible criteria which might guide the psychiatrist in making his recommendation. Special attention was paid to the help given by reports from skilled instructors. As part of occupational treatment, and as a guide to their suitability for training and employment, selected patients from Mill Hill Emergency Hospital are sent to an adjacent technical college for classes conducted by the regular staff. The classes are clerical (including typewriting and book-keeping) and engineering or mechanical (including benchwork, elementary electricity, machine drawing). The course lasts 4 weeks and enables the instructors to send individual reports on every case.

It was anticipated that the instructor's grading would correspond in some degree to the psychiatrist's decision about disposal, and that men who had done well, for example, in the mechanical course, would be posted to a mechanical job. A close correspondence could not be expected, as clinical considerations would also enter into the decision. On analysis of intelligence-grades and proportion discharged from the Army in both the group attending the courses and the total admissions to the hospital, it was found that the patients sent on the courses were intellectually, and in potential fitness for duty, superior to the general level of neurotic patients admitted to the hospital. Moreover the clerical group included more intelligent people than the mechanical, and the instructors rated the clerical group higher (either because they did better or because the standards were less severe) than the mechanical group. The proportion discharged from hospital as unfit for further service was 34 % in the clerical group and 44 % in the mechanical.

On comparing statistically the instructors' grading of men known to have been discharged within 12 months and instructors' grading of men known to be doing well in the Home Command after 12 months, it was shown that there was a significant association between the instructors' grading of patients on the clerical course, and the patients' subsequent career in the Army. Thus the doctor might profitably have given more weight to the clerical instructors' grading, but there is no evidence that paying more attention to the performance of those attending the mechanical course would have been advantageous. The instructors' grading on those who had done poorly at the courses enabled the doctor to recommend work not requiring clerical and engineering skill, and without this opinion he might have formed a mistaken opinion about the man's untried and sometimes self-proclaimed abilities.

Analysis of further criteria which might influence selection for special posting showed that previous training, experience, and interests played some part, but only in relation to other relevant considerations (chiefly clinical). A man's professed

attitude to the last Army occupation in which he was engaged before coming to hospital did not seem to have affected the recommendation as to whether he should be discharged as unfit, returned to his former unit, or specially posted by annexure. The annexure cases as a whole were found to fall midway in intelligence scores between the men discharged unfit and the men attending the special courses.

For the whole neurotic population, there was a significant association between intelligence-grade and Army retention or discharge. The less intelligent men were evidently more likely to be discharged than retained. A 12-months' follow-up of the men who had attended the courses and returned to the Army showed that 52 % were doing full duty efficiently and 33 % had been discharged as unfit. Comparison of the figures with those of the War Office follow-up of all annexure cases from the hospital during approximately the same period shows a possibly significant difference to the advantage of the men attending the special courses. It is of interest to note that 3 of the men have since attained commissioned rank.

Thus the psychiatrist's judgment of the fitness for further military service of patients who had attended the practical courses in engineering or clerical work was better than for the whole group of persons posted by annexure. Either these men were selected for the special course by criteria relevant to their future military fitness, or the guidance afforded to the psychiatrist by the instructors' reports and the salutary effects of the instruction may have been responsible. The vocational problems of the neurotic cannot be isolated, nor can they be safely left to look after themselves. This would apply to civilians in normal times as well as to soldiers now.

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NEUROPSYCHIATRY AT A ROYAL AIR FORCE CENTRE • An analysis of 2,000 cases

by S I Ballard & H G Miller, *British Medical Journal*, 2, 40-43, 8/7/44

The authors review the findings in 2,000 successive patients investigated at an R A F neuropsychiatric centre. Twenty-two per cent were suffering from organic nervous disease, and 3 % were mental defectives who had been referred for hysterical symptoms, ineffectiveness, or minor disciplinary offences. The majority (68 %) were psychoneurotics, of whom 54 % were suffering from affective disorder.

The authors point out that many of the patients had received extensive and repeated investigation for the presence of organic disease, and sometimes lengthy but fruitless courses of treatment for psychosomatic symptoms, the true nature of which readily became apparent on taking a psychiatric history.

They also stress the importance of giving explanation and reassurance with surgical treatment whenever possible, with a view to preventing the chronic neurotic sequelae which sometimes develop after surgical intervention.

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POST-OPERATIONAL STRAIN IN THE NAVY

by D Curran & G Garmany, *British Medical Journal*, 2, 144-146, 29/7/44

Psychiatric casualties attributable to operational stress occur more commonly after, than during, the stress. Thus, the psychiatric sickness-rate is much greater ashore than afloat.

The thesis put forward by Surgeon Captain Curran and Surgeon Lieutenant Garmany is that men at sea develop a condition of tension resulting in an increased responsiveness and readiness, which are physiological and appropriate, but on coming ashore, this state of tension may become pathological, because it is inappropriate or unnecessarily intense having regard to the altered and reduced tempo of the life. The greater the lag that is shown in adjusting to a tempo suitable for the environment, the more does the state that was, in special conditions, within normal physiological limits, stand out as being abnormal and pathological.

The substantial majority of these patients could be returned to duty. Symptomatic relief often follows reduction of tension by sedatives such as barbiturates, and by increasing the "tempo" by early draft to sea, before habituation has occurred.

PSYCHIATRIC CASUALTIES FROM THE NORMANDY BEACH-HEAD

by C Anderson, M Jeffrey & M N Pai, *Lancet*, 2, 218-221, 12/8/44

The authors, writing from an Emergency Medical Service neurosis centre, describe 100 psychiatric casualties received from Normandy soon after the invasion of France in the summer of 1944

They contrast the neurotic responses with those described after the retreat from Dunkirk. The 1944 cases were of high morale and were disinclined to concentrate their attention on their physical and emotional discomforts. Six were severe chronic neurotics, 5 could be described as cases of pure physical exhaustion, and 2 showed schizophrenic reactions. The rest were men with a history of childhood neurosis who had adjusted superficially in adult life but broke down under severe stress. Those who had developed neurosis in previous campaigns had more severe and more prolonged symptoms than those facing battle for the first time.

Conversion hysterical symptoms were comparatively rare, and when they did occur they affected special senses chiefly and responded very rapidly to treatment.

The early and effective sedation these men had received before arrival at the neurosis centre was considered to have played a large part in their rapid recovery.

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PSYCHOSOMATIC CASUALTIES IN THE MIDDLE EAST

by A Torrie, *Lancet*, 1, 139-143, 29/1/44

Major Torrie reviews 2500 casualties admitted to a base psychiatric hospital in the Middle East. Anxiety neurosis formed 35.6% of the total, hysteria 25.8% and psychopathic personality 10.0%. The causes leading to the final psychiatric breakdown were usually multiple, and battle experience was the culminating factor. Contributory factors included separation-anxiety, maladaptation to climatic conditions, timid temperament, low intelligence, family history, and neuropathy and previous neurosis.

A more detailed description of 1000 cases of anxiety neurosis is given, 89.9% of these were returned to duty, 58.6% to full duty, 56.0% give history of neuropathic instability in parents or siblings. Headache, anxiety, tremor, disturbed sleep, and depression were the most frequent symptoms.

Ninety-two cases of anxiety neurosis and hysteria were subjected to rapid analysis, the main aetiological factor elicited was separation-anxiety. These men exhibited feelings of insecurity with dependence on, and fear of, authority. In most cases there were situations in early childhood in which the patient could not deal with aggressive impulses aroused by threat to the safety of his emotional relationship with parent or parent-substitute. Treatment in general was eclectic, including physical, individual- and group-psychotherapy according to the particular needs of the case.

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TWO YEARS OF MILITARY PSYCHIATRY IN THE MIDDLE EAST

by H B Craigie, *British Medical Journal*, 2, 105-109, 22/7/44

Lieutenant-Colonel Craigie describes in this paper the development and organization of military psychiatry in the Middle East from its inception in August 1940. Among the psychiatric casualties, a high incidence of previous neurosis and markedly abnormal personality was found. One in five patients gave evidence of markedly psychopathic family history. There was a smaller incidence of previous neuropathy in men who broke down during battle than in cases not precipitated by battle stress. The patients encountered were of diverse races and nationalities, and in some cases they were inadequately trained. Precipitating factors were domestic separations and worries, and unfavourable climatic conditions.

Four out of 5 battle-casualties were cases of fatigue and exhaustion. In anxiety-states depression, anxiety, headache and insomnia were the most frequent symptoms. In hysteria,

the most common symptoms were amnesia, convulsions, motor symptoms and fugues. The dissociative type of hysteria (amnesia and fugues) occurred more frequently than the conversion type. Schizophrenia accounted for half of the psychotic cases.

The author emphasizes the importance of immediate treatment. Rest was procured by full sedation. Continuous narcosis was extensively used for acute anxiety-states, and intravenous barbiturates were helpful in treating hysterical symptoms by suggestion. A large proportion of patients was returned to duty and only 5-6% had to be readmitted.

The importance of prophylaxis in the form of personnel-selection is stressed, and the author believes it is useless to send men overseas when their previous history indicates that early breakdown is probable, and that, if the present system of personnel-selection had been applied from the beginning of the war, a very large proportion of the psychiatric casualties of the Middle East would have been avoided.

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INVESTIGATION AND TREATMENT OF ENURESIS IN THE ARMY

Preliminary report on 277 cases by P L Backus & G S Mansell, *British Medical Journal*, 2, 462-465, 7/10/44

The authors describe their clinical findings and results of treatment of 277 soldiers suffering from nocturnal enuresis, successively admitted to a military hospital. In addition to full physical examination, the following special examinations were carried out:

- i Bladder-function test, consisting of noting resistance to passage of catheter and measuring the volume of boric acid solution at 20 mm pressure of water required to induce desire to micturate. Two further readings were taken after the patient had been encouraged to relax his bladder. Two final volumes were measured at 40 mm and 60 mm water-pressure (referred to as distension readings).
- ii Psychiatric examination, with special reference to the history of the condition and possible psychological factors for any periods of remission or relapse.

Nocturnal enuresis had existed from infancy in 78% of cases, of which 63% had had no remission. Increased frequency and urgency occurred in 82%.

Lack of training and unhappy home conditions were regarded as the most important factors for the persistence or development in those patients with pre-service onset of symptoms. In those who developed symptoms after enlistment, failure to adapt to barrack-room life, regimentation, and battle experience, were regarded as the most important factors.

Ninety-two per cent showed no abnormality on physical examination, spina bifida was found in 10% of those x-rayed, 25% showed small bladders on cystometry. Psychiatric investigation showed 6 main personality types: timid immature dependent, 48%, average type of personality, usually showing indifference to symptoms, 27%, compensatory aggressive, 10%, pure aggressive 6%, psychopathic personality, 6%, obsessional, 25%.

Treatment consisted of explanation of the mechanism of symptoms and normal bladder-control. The degree of relaxation demonstrated on cystometry served as a useful starting point for re-educative procedures. First sphincter control with voluntary bladder-relaxation during the daytime was encouraged. Nocturnal control was put on the same basis as day control, and was fortified by autosuggestion at the time of going to sleep. When evidence of control appeared, the procedure of "self-waking" was introduced if needed.

The authors consider that suitability for treatment in the Army depends on age (preferably under 30 years), fair intelligence, a bladder of more than 300 cm³ capacity with 60 mm water-pressure, and evidence of voluntary powers of relaxation and a reasonably good attitude to further service.

The follow-up given on 40 patients is, as the authors state necessarily very incomplete, and in order to evaluate the results of treatment adequately a follow up of a large number of patients extending over a longer period would be necessary.

Problems of Senility

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A PSYCHOMETRIC STUDY OF SENILITY

by H Halstead, *Journal of Mental Science*, 89, 363-373, July-October 1943

The author investigated 38 senile patients with various psychometric tests. Starting with 80 tests, he finally chose a battery of 25 short tests, and in this paper describes the results obtained by using this battery on a group of 20 less-seriously demented senile patients (the more-seriously demented remainder are reported later)¹

The tests are divided into 3 groups according to the degree of difficulty experienced by senile patients. The most difficult tests were those in which patients were required to break away from old mental habits and adapt to unfamiliar situations, tests of recent memory, judgment, and planning, and tests embodying difficult or lengthy instructions. Less difficulty was found in tests of rote memory, fluency of association, simple arithmetic, and vocabulary. Performance seemed to be least affected in tests of visual recognition, old mental habits and simple motor tasks.

It is important that tests of senility should be short because of difficulty in maintaining attention, impaired comprehension and poor retention. Perseveration is increased, and there is usually loss of speed and steadiness in motor functions.

672

MENTAL TESTS IN SENILE DEMENTIA

by H Halstead, *Journal of Mental Science*, 90, 720-726, July 1944

Twenty-five mental tests were applied to a group of 18 patients with severe senile dementia. The results were compared with a similar investigation carried out on 20 senile patients with lesser degree of dementia (Halstead, 1943). All the tests differentiated between the two groups.

The most discriminative tests were picture-memory, reading speed, digits forward and reversed, colour naming reversed, recall of paragraph, naming months reversed.

The investigation revealed the rapid decline of recent memory span generally and of substance memory in old people, and also the fact that it is impossible to assess deterioration by short-cut methods, a variety of tests must be used to test a patient's strong and weak points.

REFERENCE

¹ Halstead, H (1943) *J ment Sci* 89, 363

¹ [BMB 671]

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SOME PROBLEMS ARISING FROM A STUDY OF MENTAL PATIENTS OVER THE AGE OF SIXTY YEARS

by F Post, *Journal of Mental Science*, 90, 554-565, April 1944

The author found that during recent years there has been a tendency for a greater increase of admission of patients over the age of 60 to mental hospitals than would be expected from the increasing age of the general population. He found that only 30 of his series of 78 mental patients over the age of 60 had previously been satisfactorily adjusted individuals. A positive family history of mental or neurotic disorder occurred in 32%.

There was a correlation between previous psychopathic tendencies and severity of psychotic symptoms (as contrasted with dementia alone). This study, in conjunction with the findings of other workers, indicates that factors other than physiological and anatomical are responsible for the origin of senile and arteriosclerotic mental disorders. Old age alone does not produce mental illness, for this to occur, predisposing constitutional factors must have been present in the patients, who had in many cases shown their tendency to nervous and mental abnormalities previously. In avoiding breakdowns in old people, early recognition and treatment of physical illness, adequate nutrition, and sleep, are important.

¹ [see BMB 672]

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CRIME, SENESCENCE AND SENILITY

by W N East, *Journal of Mental Science*, 80, 835-850, October 1944

Senescence, apart from its physical concomitants, is characterised by a gradual lessening of the intellectual, emotional, and volitional attributes of mind, whereby memory, perception, receptivity, attention, affection, interests and desires become restricted, less vivid and less compelling. It passes into senility when the impairment becomes excessive, the mental activities imperfectly synchronized, and then there is a failure of initiative, the ability to form well-considered opinions, and sustained effort, and social maladjustment results.

The development of senility in some people and not in others depends, in part, upon constitutional factors, as well as on past experiences, neurotic reactions and, indirectly, their manner of life.

Dr East points out that although aged prisoners in Britain have been for many years treated under a milder form of discipline than others, the mental background of the ageing offender before his trial is also important, but has received less attention than is due, in spite of the fact that the later period of life presents special problems to senescence and senility. Knowledge of the mental background of the aged offender may suggest the most suitable way of dealing with him and of protecting society from his misconduct.

Senescence will not acquit the offender of responsibility, though in cases bordering on senility, his mental condition may modify culpability to an extent which many medical men believe should be taken into consideration by a court of trial in determining the award, because the degree of blameworthiness present is somewhat between that which is attached to the illegal act of a mentally normal person and one who is irresponsible because of insanity.

In early stages of senile or arteriosclerotic dementia, culpability on medical standards may be modified. In advanced stages the accused may be properly considered insane according to the law.

In all cases appropriate awards or treatment can be selected only by taking into consideration, with other facts, what the aged offender was, as well as what he is.

Physical Factors in Mental Disorder

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PHYSICAL EXAMINATION OF TWO THOUSAND CASES OF NEUROSIS

by H G McGregor, *Journal of Neurology, Neurosurgery and Psychiatry*, 7, 21-26, January & April 1944

The material considered in this paper consists of 2,228 consecutive admissions to a military hospital for neurosis. Seventy-eight of the patients were found to be suffering from organic disease which had, in the first instance, been mistaken for neurosis. Contributory or minor ailments were found in 35% of cases. The most common presenting symptoms were anxiety, dyspepsia, effort-intolerance, "rheumatism," and hysterical symptoms.

A special study was made of blood-pressure. Fahrenkamp (1931) and Mohr (1925) found that systolic blood-pressure may vary as much as 50 mm Hg under the influence of emotion, and isolated readings of 160 and 170 were not uncommon. Fourteen per cent of the present group had blood-pressure higher than 140 mm Hg systolic and 90 mm Hg diastolic pressure. Lower readings were, in most cases, found on retesting after a period of rest. With the exception of 7 cases, it was possible to obtain diastolic readings below 100, while the systolic fell to a more normal level—usually though not always, to 140 or less. All 7 cases showed abnormalities in retinoscopy, urine analysis or renal function tests.

It was concluded that a systolic blood-pressure reading up to almost 200 mm Hg may be within normal limits, providing that the level is not maintained and the diastolic pressure is not higher than 100. A diastolic reading which

exceeds 100 is almost certainly pathological. No correlation was found between blood pressure and external signs of anxiety.

The unreliability of the exercise-tolerance test in effort-syndrome cases is pointed out. Most patients improved in the exercise-tolerance test after 2 days of light physical training. The discrepancy is regarded as being due to emotional factors.

The author discusses factors which influence localization of symptoms under the headings (i) heredity, (ii) constitutional, (iii) incidence of previous disease or trauma, (iv) physique-personality. The majority of patients had been timid for the greater part of their lives. There was often a history of chronologically remote trauma at the site of the neurotic symptom. These factors only direct the location of the symptoms, which are primarily psychogenically determined.

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SOMATIC MANIFESTATIONS OF PSYCHONEUROSIS

by I. Douglas-Wilson, *British Medical Journal*, 1, 413-415, 25/3/44

Captain Douglas-Wilson points out that the striking feature of psychoneurosis observed in the services during this war has been the frequency with which somatic symptoms are presented. As the underlying mental disorder is revealed only by direct enquiry, such cases are commonly sent to the general physician. Cook & Sargant (1942) pointed out that the negative method of arriving at a diagnosis by exclusion is both costly in time and money and harmful to the patient. Usually a positive diagnosis can be made after taking a psychiatric history.

Out of 810 patients sent for a medical specialist's opinion at a military hospital in England, 231 were diagnosed as psychoneurotic, and of these 202 had somatic symptoms. It was found that 92 % of these were predisposed to mental illness, and with one exception the symptoms developed without the strain of actual warfare. Cardiac symptoms, dyspnoea and headache were the most frequent presenting symptoms.

Suggestion, by long confinement to bed and warnings to avoid exertion, had usually played a part in the production of cardiac symptoms. Respiratory symptoms were often associated with fear of tuberculosis. Urinary symptoms were found chiefly in immature types who had particularly missed their home environments.

Symptoms often co-existed in more than one system. For example, nearly half of the 178 patients who did not primarily claim cardiac symptoms reported as subsidiary complaints dyspnoea, palpitations or precordial pain. Important factors determining the localization of somatic symptoms were existing trivial organic disorders, previous personal or family history of organic disease in the affected system, and recall of earlier warnings by doctors and relatives about the condition of the system involved.

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PAROTID GLAND SECRETION IN AFFECTIVE MENTAL DISORDERS

by H. J. Eysenck & P. M. Yap, *Journal of Mental Science*, 90, 595-602, April 1944.

Parotid gland secretion is one of the most easily observable manifestations of autonomic activity, and should be helpful both in the elaboration of the theory of autonomic activities and perhaps also in practical diagnosis (Eppinger, 1917; Sachs 1936; Guillaume, 1928). Strongin & Hinsie (1938) found that manic-depressive patients secreted less saliva than normal controls.

Dr Eysenck and Mr Yap tested the hypothesis that affective disorders, both neurotic and psychotic, are associated

with a relatively decreased salivary secretion, and also the findings of Brunacci & de Sanctis (1914), who were the first to show that mental work had an inhibitory effect on salivary secretion. Lashley (1914) on the other hand found that mental work had a stimulating effect.

For measurement of the secretion of the parotid gland, the subject was seated in a chair, reassured about the purpose of the experiment, and encouraged to assume a comfortable position. Copious secretion, to facilitate the fixing in the right position of a small disc similar to that developed by Lashley (1914, 1916) was ensured by dropping some lemon essence on the tongue of the patient; the disc was then firmly held over the opening of Stensen's duct by suction produced by inhaling on a tube leading from the outer chamber of the disc. From the inner chamber of the disc a small rubber drainage tube passed through the corner of the mouth of the subject, carrying the secretion to the actual measuring device which was modified from Richter & Wada's (1924) description. In this device the saliva is drained off through a long thin horizontal glass tube calibrated in mm, and the actual progress of the saliva is indicated by means of an air bubble introduced through a T-connection.

The authors measured parotid secretion in a group of 100 neurotic and psychotic patients of both sexes. It was found that the salivary secretion in neurotic patients suffering from affective disorder (anxiety, depression) was significantly lower than that of neurotic patients suffering from hysterical and other non-affective disorders.

Similarly in psychotics, those suffering from affective disorder (melancholia, manic-depressive psychosis), showed a significantly smaller secretion than the group of schizophrenics and other non-affective disorders. It was also found that mental work decreased salivary secretion. In fact there was 10 times as much salivary secretion during silent reading as there was during very concentrated mental work.

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HYPOGLYCAEMIA AS AN EXPERIMENTAL PSYCHOSIS

by W. Mayer-Gross, *Proceedings of the Royal Society of Medicine*, 36, 343-348, May 1943.

The value of drugs in producing experimental psychoses has been demonstrated repeatedly, mescaline being the outstanding example. The utilization in the same way of hypoglycaemia produced by insulin is carried a stage further in this report. Mayer-Gross has found that attempts to relate the sugar level in the cerebrospinal fluid to the clinical condition can be falsely interpreted unless allowance is made for the time-lag of 15 to 30 minutes before the sugar level in the cerebrospinal fluid corresponds to that in the blood. When this was taken into account, the cerebrospinal fluid-sugar level proved to be a less reliable indicator of clinical symptoms than the blood-sugar level. Twenty minutes after an intravenous glucose injection which raised the blood sugar to more than 200 mg. per 100 cm.³ and awakened the patient completely the sugar in the cerebrospinal fluid was at almost the same level as it had been before the injection of glucose. The reported observations deal particularly with the stage of akinetic mutism, and sensory anomalies. The signs of autonomic excitation and motor symptoms are also described with emphasis on differences between individuals. A phylogenetic explanation for the climbing movements with which reflex grasping of the hands and fingers is always associated is put forward on lines similar to those formulated by Foerster for congenital athetosis. Mayer-Gross considers that the striate body cannot be wholly responsible as hyperkinetic behaviour in hypoglycaemia is so graceful and differentiated as to imply the participation of the motor cortex.

RETURN OF VIRILITY AFTER PREFRONTAL LEUCOTOMY WITH ENLARGEMENT OF GONADS

by R E Hemphill, *Lancet*, 2, 345-346, 9/9/44

Prefrontal leucotomy was performed on a long-standing case of obsessional neurosis, impotence and hypogonadism. The physical effects of the operation were immediate, weight was gained, and the external genitals grew rapidly and steadily until the maximum development for the man's height and build was attained. That this was directly due to the operation is considered certain, as both weight and genital atrophy had remained unchanged for years in spite of other treatment. There was increase of weight from 6½ stones [about 42.6 kg] before the operation to 10¾ stones [about 66.2 kg] 4 months later.

The clinical picture in the last stage was consistent with the diagnosis of pituitary insufficiency (perhaps secondary to prolonged inanition) leading to atrophy of testes and low output of 17-ketosteroids. After operation the output of 17-ketosteroids increased and sexual behaviour was normal.

The author assumes that in cutting white fibres passing dorsally, from the frontal cortex, the hypothalamus or pituitary was released from inhibitory influences. He considers that the dramatic result probably represented a correction of deficiency rather than a hyperfunction. The restoration of the gonads was probably effected by liberation of gonadotrophic, corticotrophic and other anterior-pituitary hormones, and this would account for increased secretion of 17-ketosteroids.

The Comparative Method in Neurology

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DISCUSSION ON THE LIMITATIONS AND USES OF THE COMPARATIVE METHOD IN MEDICINE IV NEUROLOGY AND PSYCHIATRY

by E Jones, D S Russell, J R M Innes, W S Gordon, W H Andrews & C L Oakley, *Proceedings of the Royal Society of Medicine*, 37, 651-658, September 1944

Dr Ernest Jones pointed out that the findings of psychoanalysis carry the theory of evolution to its logical conclusion by treating both mind and body from a genetic point of view. Instincts are essentially conservative in nature, in that their aim is to reinstate as far as possible some earlier state of affairs. A similar tendency occurs in psychopathological conditions, namely the tendency to regress or to revert to earlier stages in ontogenetic and possibly phylogenetic development.

The pleasure-pain principle is more comprehensive than psychologists used to think. Brun and other biologists have produced evidence, chiefly among insects, which strongly supports the belief that there are physical tendencies comparable to the pleasure-pain principle of mental function. There are extreme cases where organic search for pleasurable sensations has overwhelmed other tendencies, with most deleterious or even fatal results to the species concerned.

Dr Dorothy Russell described the advances made in comparative neurology by the following animal studies. The study of developmental anomalies in animals to elucidate kindred conditions in man, experimental trauma in the study of concussion and the healing of wounds, the experimental production of demyelination by poisons, animal experimental methods of studying industrial intoxication and of vitamin deficiencies, experimental tumour-production, and therapeutic trials in animals of such substances as acridine antiseptics, sulphonamides and penicillin.

Dr J R M Innes pointed out that work on animal virus-encephalitis had contributed greatly to the understanding of encephalitis and neurotropic viruses in man. Similarly the study of malformations in animals may help in under-

standing the working of the human body in health and disease. He quoted the work of Hurst, who found that cyanide and sodium azide produced demyelination, and that the lesions produced were similar to those found in spontaneous equine leuco-encephalitis occurring in America and believed to be due to a toxic factor in damaged fodder.

He also pointed out that certain stages of swayback disease in lambs resembled the anatomical picture of Schilder's disease in infants. Swayback disease is regarded as being due to copper deficiency, and can be prevented by giving copper to pregnant ewes. It remains to be seen whether further studies of this condition will help to elucidate the aetiology of idiopathic human demyelination disorders.

Dr W S Gordon described the disease louping-ill, and the discovery that it was caused by a tick-borne virus. The disease can readily be prevented by subcutaneous inoculation of susceptible sheep with formalinized 10% saline suspension of infected brain and spinal-cord tissues. The disease is similar in many respects to poliomyelitis, and it has been reported in man. The discovery of a new disease "tick-borne fever," found during the investigation of louping ill, is also described.

Dr W H Andrews dealt with the effects of intoxications on the nervous systems of animals, and noted the interesting differences of symptoms which may be shown even by closely related species of animals, e.g. difference between dogs and cats in reaction to morphine. The effects of snake- and plant-poisons in animal nervous systems are also described.

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DISCUSSIONS ON THE LIMITATIONS AND USES OF THE COMPARATIVE METHOD IN MEDICINE. V COMPARATIVE PSYCHOLOGY AND ANIMAL BEHAVIOUR

by C S Myers, W H Thorpe, D B Johnstone-Wallace, K Kennedy, A Walton, J Hammond, E S Stern & M R A Chance, *Proceedings of the Royal Society of Medicine*, 37, 658-662, September 1944

Dr C S Myers stressed the need for observing instincts arising or disappearing through mutations or under other conditions, e.g. transitory appearance of phylogenetically-old instincts during ontogeny. He drew attention to the distinctive characteristics of instincts at different levels of animal life, and especially to the degree to which, in man, intelligence has usurped the functions of specific inherited behaviour, while at the same time the instinctive nature of the general determining direction of behaviour is preserved and clearly recognizable.

Dr W H Thorpe discussed the types of animal learning and their relation to the problem of instinct. He classified learning into habituation, associative learning, latent learning, insight learning, and imprinting. The first and last of these were related to the problem of instinct. Habituation enabled the animal to learn to ignore those mild stimuli which proved, after all, to be harmless or of no significance.

Imprinting was a special type of learning occurring primarily in animals which did not recognize their own species instinctively. Through it, the young animal came to respond to those highly elaborate patterns of behaviour which are characteristic of its species. Imprinting therefore resulted in the acquisition of the biologically "right" object of the social reactions.

Professor D B Johnson-Wallace & Captain Keith Kennedy (both of Cornell University, USA) described an investigation of grazing-management practices and their relationship to the behaviour and grazing habits of cattle.

Dr Arthur Walton (School of Agriculture, Cambridge) spoke on comparative sexual behaviour in the male. He believes that an animal's behaviour is, in very large measure, determined by anatomical structure, and quoted a number of interesting examples of sexual behaviour in support of the thesis. The effect of conditioned inhibitions in producing decline in potency and virility in bulls after continued use was also discussed.

BOOKS, MEMORANDA, REPORTS

[The prices quoted are those which obtain within the United Kingdom. Editors of medical journals who wish to review publications of which notices appear below are invited to apply to the Editor for review copies of which a few are sometimes available. Orders for any of the publications mentioned below may be sent to the Editor if there are difficulties in obtaining them locally. Publications may be referred to by the numbers used below, preceded by the letters BMB, e.g. BMB 606/99. It should be noted that supplies of all publications are limited and there can be no certainty that publications ordered or requested for review will be available.]

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A PATHOLOGY OF THE EYE

by E. Wolff. Second edition. London, H. K. Lewis & Co. Ltd., 1944. 285 pages, 212 illustrations. £2 2s. [£2.1]

The first edition of this volume appeared in 1935 and the author has well utilized the opportunity of a second edition to strengthen the book. There are now 212 illustrations instead of 124 and they help materially the presentation of what is essentially descriptive text. The book is a sound and adequate guide to the morbid changes occurring in the eye. The first edition contained a considerable amount of matter of a purely clinical character, in the present volume this has been largely deleted, making room for additional descriptions of morbid processes. The excisions appear to have been too drastic in some places, as for instance in the chapter on errors of refraction, which has now become reduced to a single page dealing exclusively with myopia. In a subsequent edition the author might well consider the incorporation of matters bearing on the pathology of the eye in its broad aspects. Morbid anatomy and pathology are not synonymous.

Chapter headings: (i) diseases of the cornea, (ii) diseases of the conjunctiva, (iii) diseases of the lids, (iv) diseases of the uveal tract, (v) diseases of the lens, (vi) the vitreous, (vii) the retina, (viii) glaucoma, (ix) the sclera, (x) injuries to the eye, (xi) congenital anomalies, (xii) intraocular new growths, (xiii) the optic nerve, (xiv) the orbit, (xv) diseases of the lacrimal organs, (xvi) errors of refraction, (xvii) eye changes in diabetes, (xviii) some points in general pathology. There is an excellent bibliography and a full index.

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FRIENDS' AMBULANCE UNIT

Fifth Annual Report, 1945

published by the Friends' Ambulance Unit, 4 Gordon Square, London, W.C. 1, 1945. 23 pages, illustrated.

The Friends Ambulance Unit was started by members of the Society of Friends (Quakers) and others. It is a voluntary body, composed principally of volunteers who object on grounds of conscience to serving in the armed Forces and who have been granted exemption from such service. The Unit consists of about 800 men and women, many of whom are unpaid and of whom one-third are Quakers.

This annual report of the FAU shows that the Unit has continued its important work in every theatre of war. Civilian relief work includes the organization of shelter, nourishment and medical aid to as many as 5,000 refugees per week in France, Belgium and Holland. Similar work has been carried out in Italy and Sicily. In Syria and Ethiopia, emergency medical services have been carried on despite lack of a public spirited social conscience among the people, and other difficulties. The apathy and superstition of people in these regions is being countered by instruction in public health and general education in schools.

In India Unit members have been active in the relief of distress caused by flood and famine. They have been able to organize the daily feeding of over 7,500 people and to help with the distribution of supplies to thousands more. Similar work carried out in Free China has been supported by financial help from United China Relief and other Funds. This work has been carried on despite appalling transport and other difficulties. FAU medical teams are working in Chinese hospitals close to the Yunnan front. The comparatively small number of members of the FAU serving in China is making a great contribution towards the alleviation of the present incalculable suffering in that country.

A considerable proportion of the Unit personnel has been engaged in military medical work in the forward battle areas. In Britain over 100 members have submitted to experiments concerning various branches of medical research—the efficacy of antimalarial drugs, oligæmic shock, the physiology of acclimatization to tropical conditions, nutrition experiments and scabies prophylaxis.

This great venture in faith in the midst of war in Britain, Europe, the Middle East, Ethiopia, India and throughout Free China has not been carried on without loss and of 21 members captured by the enemy, one has died and ten remain in prison camps to carry on their work among prisoners of war. Work by pacifists in close co-operation with the Army cannot be undertaken without difficulties on both sides. Such difficulties seem to have been overcome and the military authorities have greatly appreciated the many services which the Unit has been able to render.

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AN ANNOTATED BIBLIOGRAPHY OF MEDICAL MYCOLOGY, 1943

edited by S. P. Wiltshire, in collaboration with C. Wilcocks & J. T. Duncan. Kew, Imperial Mycological Institute, 1944. 32 pages. 5s. [£0.25]

Reference to the widely scattered literature on medical mycology becomes much easier with the publication of this bibliography.

It attempts a complete survey of the papers on the subject published in 1943 or noted by abstracting journals during that year. There is no systematic arrangement of entries, but adequate author and subject indexes are provided. Each entry includes either a brief annotation or a reference to where an abstract may be found.

The bibliography is sponsored by the Imperial Mycological Institute of which its senior editor is director. It is to appear annually and will be welcomed as a useful addition to the reference section of every medical library.

682/111

MEDICO LEGAL BLOOD GROUP DETERMINATION

Theory, Technique, Practice

by D. Harley. 2nd impression. London, William Heinemann (Medical Books) Ltd., 1944. 119 pages, 5 plates. 12s. 6d. [£0.625]

This is the first monograph in English on the subject. The present volume is a reprint of the first edition, published in 1943. It shows that blood grouping for medico-legal purposes has not developed in Britain to such an extent as elsewhere. The book incorporates all important work on the history, genetics and serology of forensic blood grouping and should therefore prove of value to those working on this subject. The technique of collecting, and testing of blood, semen and saliva, and the interpretation of results is described in detail, and attention is drawn to the fact that the ABO group is detectable in these secretions as well as in blood. Particulars of the author's experience of tests in cases of disputed paternity and in criminal cases are reported, and the present position regarding the legal application of such tests is given, together with relevant reports and proceedings.

The chief obstacle in Britain to the more general use of blood tests in cases of disputed paternity is the lack of legislation enabling courts to order the performance of these tests. To overcome this, the Bastardy (Blood Tests) Bill was drafted in 1938. After consideration by Parliament it was submitted to a Select Committee. Before the Bill became law, the present war made it necessary to postpone much of the business occupying Parliament and the Bill lapsed. Both the Bastardy Bill and the report of the Select Committee upon it are reproduced in full.

Chapter headings: (i) the ABO system of blood groups, (ii) heredity of the ABO system, (iii) the MN system of blood types, (iv) blood group antigens in tissues other than blood, (v) medico-legal application of blood group tests, (vi) general technique paternity tests, (vii) blood and secretion stains, (viii) disputed paternity, (ix-x) blood and secretion stains.

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HEALTH AND SOCIAL WELFARE, 1944-1945

Advisory editor, The Rt. Hon. Lord Horder. London, Todd Publishing Co. Ltd., 1944. 334 pages. £1 1s. [£1.05]

With the appearance of this publication a new and important annual reference book, of especial value to medico-social welfare workers, becomes available. Section 1 contains the following short articles: (i) Public health to-day and to-morrow (Sir Arthur MacNalty), (ii) Summary of the Report on Social Insurance and Allied Services (Sir William Beveridge), (iii) Planning for health (Edith Summerskill), (iv) The British Medical Association and the medical services (Charles Hill), (v) State medicine (Somerville Hastings), (vi) Progress in public health 1844-1944 (M. Caston), (vii) Education in England yesterday to-day and to-morrow (H. C. Dent), (viii) The school medical service (J. E. A. Underwood), (ix) Food: the basis of existence. In section 2, specialized articles describe rehabilitation, public assistance, family allowances to-day, the development and scope of industrial welfare work, the treatment of juvenile delinquency, developments in drugs, dentistry and public health and good eyesight and well-being. While section 3 outlines the Beveridge Report on Social Insurance, the Report of the Inter-departmental Committee on Rehabilitation, the Norwood Report on Curriculum and Examinations in Secondary Schools, the Report on the Abolition of Tuition Fees in Grant-aided Secondary Schools (Fleming Report), the Report of the Advisory Council on Education in Scotland and the Report of the Youth Advisory Council on the Youth Service after the War.

The development of health legislation is discussed in section 4, while, in section 5, further short monographs outline the New Zealand health and social services, the Soviet health and social welfare services and the social development of the British Colonial Empire. A valuable series of official directories of the various Ministries concerned in health and social welfare in Britain forms section 6 of the book, and these bodies are given the opportunity of outlining their several policies in section 7. Section 8 gives the statements of policy and work of the British Dental Association, British Medical Association, Central Council for Health Education, Central Council of Recreation, Physical Training, Eugenics Society, Food Education Society, Industrial Health Research Board, London School of Hygiene and Tropical Medicine, Medical Research Council, Miners' Welfare Commission, National

Association of Boys' Clubs, National Association of Girls' Clubs, National Baby Welfare Council, National Institute of Industrial Psychology, National Playing Fields Association, National Smoke Abatement Society, Noise Abatement League, Royal Institute of Public Health and Hygiene, Royal Sanitary Institute, Scottish Council for Health Education, Women Public Health Officers' Association. Next (section 9) the names and addresses of organizations interested in health and social welfare are recorded. Lists of suitable books, periodical publications and films comprise section 10, and some interesting vital statistics and other tables are given in section 11. The book is completed by a short "Who's Who in Health and Social Welfare".

This publication, which was urgently needed, succeeds admirably in bringing together in convenient form a large amount of information. It is the first attempt at a reference book on the subject and a few omissions will no doubt be noticed by the careful reader. The list of books (section 10) appears to need revision, one hardly expects to find technical works of the calibre of Bigger's *Bacteriology*, Barclay's *Digestive tract* and Walshe's *Nervous system* included in a bibliography intended for the non-medical reader. The advice of the Association of Special Libraries and Information Bureaux (ASLIB) might be sought in this connection. Telephone numbers would be a useful addition to the list of organisations (section 9) and elsewhere. A full index would enable more speedy reference to the book. Hospital almoners are not mentioned although they will find this one of their most valuable reference books.

This is to be an annual publication. If the publishers can keep it up to date it will prove invaluable to social welfare workers and indispensable to all public and other reference libraries.

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BATTLE FOR HEALTH A Primer of Social Medicine

by Stephen Taylor London, Nicholson & Watson, 1944 128 pages, 91 photographs & 13 charts 5s [£0 25]

The prologue to this book reminds us that "The Battle for Health unites all men everywhere in a common struggle. It is no academic objective, but something which affects the life and happiness of every one of us. And it is a battle in which all must play their part." The author is a doctor who gave up clinical medicine, believing that the majority of the health problems of his patients were economic, sociological or psychological in origin. The book describes how the battle for health has been fought in the past and how it can be won in the future. Dr Taylor believes that factual information is necessary before social advance can be made, his book is therefore addressed to the layman rather than to the doctor, its aim being to impart some knowledge of the social aspects of medicine to those who are prepared to put such knowledge to practical use. Important events in the history of preventive medicine are briefly described and a more detailed account of the present health services in Britain is included. These services are a series of compromises and makeshifts, which do not appear to be very good on first acquaintance, but which work well in practice. They are not planned for all time, but for to-day, and they are capable of modification to suit changing needs. Nevertheless, they can be made much better, and this book gives many suggestions for their improvement.

The author believes whole-heartedly in the principles elaborated in the Government's proposed scheme for a national health service, and he urges the importance of a better food supply, better housing, distribution of wealth more in accordance with needs, and the wider dissemination of knowledge regarding the laws of health. The anomalies in the present method of recruiting doctors have, among other things, resulted in an insufficient supply of newly qualified doctors each year. Various improvements in medical education suggested in this book include selection of medical students solely on ability and without reference to financial means, and greatly increased facilities for the training of women doctors.

This stimulating book will prove especially valuable to the public as an interpretation of what they should expect of a state medical service. The illustrations and *Isotype* charts are admirable, and great care has obviously been devoted to the general design and lay-out of the book.

Chapter headings (i) introduction, (ii) the battle-field reviewed, (iii) the enemy examined, (iv) typhoid, (v) small-pox, (vi) rabies, (vii) tuberculosis, (viii) diphtheria, (ix) rheumatic heart disease, (x) venereal disease, (xi) death among infants and children, (xii) the knife, (xiii) man-power and organisation, (xiv) planning for health.

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MEDICINE AND MANKIND

by Arnold Sorsby London, Watts & Co, 1944 116 pages, 24 illustrations 2s 6d [£0 125]

This authoritative and lucid outline of the biological and social significance of medicine is an abridged version of the fuller work which appeared under the same title in 1941. The meaning and mechanism of health and disease are explained in non-technical language, so that the book will appeal to the general public as well as to the medical reader. The book traces the development through the centuries of methods of treatment, both individual and collective, and considers the victories gained and defeats sustained by medicine as a social force. Medicine is visualized as a living force in a changing world, and in its study it is necessary to take into account not only man's internal make-up but also his environment and his interaction with it.

This is an excellent sketch of the aims and scope of modern scientific medicine.

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ELEMENTARY ANATOMY AND PHYSIOLOGY

by J Whillis Second edition London, J & A Churchill, Ltd, 1944 280 pages, 93 illustrations 15s [£0 75]

Human anatomy is a vast subject, likely to bewilder the student unless he approaches his study of it in the right manner. It is essential for him to have a knowledge of the whole subject in broad outline before he can properly pursue a more detailed study of each organ, system and region. A good introductory manual, which will prepare the ground for the fuller text-book, is therefore advisable, to amplify instruction received in lectures. Such a purpose is admirably fulfilled by the book now reviewed. Its author is attached to the anatomy department of Guy's Hospital Medical School. In order to correlate structure with function, some elementary physiology is included, and numerous illustrations of semi-diagrammatic type supplement the text. The British revised terminology is used in the anatomical descriptions, supplemented, in the text and index, by the older names.

The text has obviously been written with great care, the illustrations are admirably executed and a model of simplicity. The book will appeal to all commencing the study of human anatomy and physiology.

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THE PHARMACOLOGY AND THERAPEUTICS OF THE MATERIA MEDICA

by W J Dilling 18th edition London, Cassell & Co, Ltd, 1944 625 pages 14s [£0 7]

Earlier editions of this book, written by J M Bruce & W J Dilling, appeared under the title *Materia medica and therapeutics*. The book, which first appeared in 1884, provides a considerable amount of information on the pharmacological actions, methods of administration and therapeutic uses of currently accepted drugs and other therapeutic agents. This edition has been revised to include the most recent advances. Several new sulphonamides have recently been introduced, and these are mentioned, together with information on penicillin, chloroxylenol as an antiseptic, mapharside in syphilis, diphenan and phenothiazine as antihistamines, benzyl benzoate and derris in scabies, pyridoxine hydrochloride in muscular dystrophies, acetomenaphthone as a source of vitamin K, thiouracil in thyrotoxicosis, and pethidine as an analgesic. Pharmacopoeial names have been substituted for many remedies previously described under trade names, and details of drugs which have become official in the third-sixth addenda to the 1932 British Pharmacopoeia are given in an appendix.

The arrangement of the matter is not systematic, and the reader will not derive from it a coherent idea of the subject. For this reason, its value is chiefly as an occasional source of information on the uses of particular drugs. Some of the references to indications for drugs are uncritical. For example, the statement that testosterone "has been advised in prostatic hypertrophy if it may be due to lack of male hormone" is evasive and does not tell the reader what he would wish to know—that is, whether this treatment has a good scientific basis or not.

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MEDICAL SCIENCE AND PHYSICAL EDUCATION

A Three-part Interim Report by the Research Board for the Correlation of Medical Science and Physical Education. Published by the Research Board for the Correlation of Medical Science and Physical Education and the Ling Physical Education Association, Hamilton House, Bidborough Street, London, W C 1, 1944 139 pages. 2s [£0 1]

The Research Board came into being on 13 July 1943, its aims being (i) to ensure more general recognition of the need for health and physical education, (ii) to achieve more co-ordination between authoritative groups dealing with various aspects of the subject, (iii) to pool the experience of national groups so that it may be of use to all, (iv) to conduct enquiry and research into questions affecting national welfare, especially those arising in connection with maternity and child welfare, (v) to put into effect and/or co-operate in practical measures likely to promote the correlation of medical science and physical education, (vi) to collaborate with appropriate international organizations or to initiate appropriate work of an international character where and when it appears opportune, (vii) to do all such things as are incidental or the Research Board may think conducive to the attainment of the above objects or any of them. The membership of the Research Board consists of representatives of organizations, and of individuals concerned with the achievement and maintenance of health.

The Policy Committee which directs the Research Board decided to subdivide the problem into four sections, (i) maternity and child welfare, (ii) education and recreation, (iii) the Services, (iv) industry, and this report is in the nature of a preliminary technical survey of these subjects, the investigation of which has involved, among other things, visits to educational, industrial, Service and other centres.

Recommendations regarding the first three subjects are incorporated in the report.

The chairman of the Research Board is Brigadier Frank Howitt, who contributes a foreword to the report.

THE REHABILITATION OF THE INJURED

Occupational Therapy

by J H C. Colson London, Cassell & Co., 1944 226 pages, 196 illustrations. 15s. [£0.75]

This is the first of a series of books which the author is writing under the general heading of *The rehabilitation of the injured*. Occupational therapy is dealt with first, not because it is more important than remedial exercises, recreational therapy or physiotherapy, but because the author believes it to be the subject about which there is the greatest lack of practical guidance, further, the demand for occupational therapists exceeds the supply, and there is need for such a book as this, which presents occupational therapy as a disguised form of remedial exercise, used for the re-education and redevelopment of specific muscle groups and the mobilization of specific joints.

In an early chapter the author outlines the basic principles of remedial exercises and shows how these can be preserved in occupational therapy. Next follow a number of chapters, each dealing with an occupation as therapy and each discussing (i) "remedial use," which deals with indications, aims, craft analysis, and remedial application, (ii) "craft technique," which gives working instructions for those who wish to learn the occupation, this section is amplified by (iii) "constructional work." The book is essentially practical in outlook, the occupations included range from simple handicraft to such everyday tasks as domestic work, gardening and log sawing. The basic movements of the occupations are analysed, so that their use as remedial exercise can be estimated, methods of adapting them for different injuries are described, together with details of the construction of original apparatus. Detailed instructions are given for those wishing to learn the various forms of craftwork included.

This is one of the first books of its kind. It will be welcomed by the surgeon, the occupational therapist and the physiotherapist. In a book of this type, illustrations are of major importance, and the author has included some admirable half-tones and diagrams. In a foreword to the book Mr E. A. Nicoll, Director of the Berry Hill Hall Rehabilitation Centre, writes that he is "convinced that occupational therapy, used intelligently and in its proper relation to remedial exercises and recreational therapy, is a valuable part of any system of rehabilitation." This book should make all who are responsible for the treatment of injuries aware of the possibilities of occupational therapy. It is clearly written and comes at a time when such information as it contains is particularly in demand. It is an important addition to the literature.

Section headings: (i) the theory of specific or remedial occupational therapy, (ii) the theory of non specific or diversional occupational therapy, (iii) resettlement in employment, (iv) handicrafts as specific or remedial occupational therapy (knitting, netting, tablet weaving, seating, basketry, weaving, fretwork), (v) industrial productive work as specific or remedial occupational therapy, (vi) woodwork as specific or remedial occupational therapy, (vii) gardening as specific or remedial occupational therapy, (viii) domestic work as specific or remedial occupational therapy, (ix) timber work as specific or remedial occupational therapy.

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OLD AGE

Some Practical Points in Geriatrics

by T H. Howell London, H. K. Lewis & Co., Ltd., 1944 50 pages. 4s. 6d. [£0.225]

It is 220 years since Sir John Floyer wrote *Medicina gerocomica*, the first book dealing with geriatrics. Comparatively little has since been published, and to-day only a small amount of literature is available on a subject which increases in importance in proportion to our ability to keep alive until old age many who would formerly have succumbed to illness in earlier life. The observations which form the basis of this book are of a purely clinical nature, and were made by the deputy physician and surgeon of the Royal Hospital Chelsea. [The Royal Hospital was founded by Charles II as a home for discharged soldiers with a service, disability or campaign pension.]

It is estimated that in 1971, men over 65 and women over 60 will account for over 20% of the population of Britain, and the author points out the increasing importance of the study of old age and its diseases. The usual clinical procedures need modification when senile patients are concerned. Certain symptoms have greater significance in such patients. Degenerative changes, chronic infection, rheumatic disease, cardiovascular disorders and cancer are predominant among the diseases of aged patients, and this small book is in effect a series of essays on these conditions written by one who is an authority on the subject.

Chapter headings: (i) approach to old age (ii) care, comfort and management (iii) temperature in old age (iv) blood pressure (v) rheumatic disease and physiotherapy (vi) chronic bronchitis, (vii) cardio-vascular diseases, (viii) progressive cerebral ischaemia (ix) the incidence of cancer, (x) disease and prognosis.

682/120

DEEP MASSAGE AND MANIPULATION ILLUSTRATED

by J Cyriax. London, Hamish Hamilton Medical Books, 1944 242 pages, 98 illustrations. 15s. [£0.75]

This is essentially a book for student and practising physiotherapists. It is the work of the assistant medical officer of the Physiotherapeutic Department, St. Thomas's Hospital and is concerned with the description of those manual techniques, both

frictional and manipulative that affect deep structures. The book is based on the author's view that when massage is required for deep-seated tissues it must be given with penetrating effect, that deep friction must be used rather than superficial massage. This requires close co-operation between doctor and physiotherapist, so that the latter may be given a detailed diagnosis especially in the light of present knowledge of referred pain.

In demonstrating the principles of deep massage and manipulation, illustrations are as essential as the written word, in this book the author has presented an admirable and extensive series of photographs to amplify his accounts of the more common procedures involved in the treatment of deep-seated soft-tissue lesions by massage. The techniques themselves are described in detail, the exact points at which treatment should be applied, duration and frequency of sessions of treatment and indications for the employment of ancillary methods, are set out for the first time.

The book is divided into two sections, in the first, the scope and purpose of deep massage and the principles governing its use are described, in addition, there are short chapters on (i) the physiotherapist and her hands, (ii) the physiotherapist's working day, (iii) the action of massage. Part two forms the greater portion of the book and consists of 98 full-page photographs, with detailed descriptions on facing pages. These descriptions include indications and contra indications for treatment, the patient's posture, technique and duration of treatment, results.

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A MANUAL OF OPHTHALMOLOGY FOR MEDICAL OFFICERS

by B W Rycroft London, Hamish Hamilton Medical Books, 1944 95 pages, 59 illustrations. 15s. 6d. [£0.525]

This work is intended as an introduction to ophthalmology, and is written for medical officers in the Armed Forces. It is confined to a description of the diagnosis, treatment and prevention of those affections of the eye and orbit which they are most likely to encounter. The writer, who is Surgeon and Dean, Royal Eye Hospital London, is at present Adviser in Ophthalmology to the British North African Forces. His book embodies the most recent experience among both home and overseas troops, in temperate and tropical conditions. Methods of examination and first-aid treatment, as well as treatment that does not require special skill or apparatus, are described in detail. The illustrations are mainly diagrammatic and concentrate on essentials, their interpretation will present no difficulties to those without previous knowledge of ophthalmology.

The book should prove most useful to medical officers in the Navy, Army and Air Force who, without previous ophthalmological experience, may be called upon to deal with disorders of vision and diseases and injuries of the eye and orbit. Chapter headings: (i) methods of examination, (ii) methods of treatment, (iii) diseases of the eye (iv) diseases of the lachrymal apparatus, (v) special subjects—night vision, stereopsis, colour vision, preventive ophthalmology, sympathetic ophthalmia, war gases, (vi) ophthalmology on active service. There are appendices giving (i) prescriptions, and (ii) nomenclature of diseases of the eye.

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A SYNOPSIS OF HYGIENE

by G S Parkinson. Eighth edition. London, J & A. Churchill, Ltd., 1944 719 pages, 16 illustrations. £1 5s. [£1.25]

Until the appearance of the seventh edition of this book, it was produced by Sir Wilson Jameson in collaboration with Dr Parkinson, and is perhaps better known as 'Jameson and Parkinson'. The last two editions have been solely the work of Dr Parkinson, who was until recently attached to the public health department of the London School of Hygiene, and he has maintained the high standard of a book which is now without equal in its particular field. Although entitled a synopsis it contains a very full account of all matters relating to public and personal hygiene. The fact that a new edition has appeared two years after the last is evidence of the many changes that have taken place, no doubt due mainly to the stimulus of war-time conditions. The material is arranged under the following section headings: (i) public health administration and the collection of vital statistics, (ii) prevention and control of disease, occupation and health, notes on animal parasites, hospitals disinfection, (iii) infant mortality, maternal mortality, maternal and child welfare, school hygiene, (iv) personal hygiene, (v) food, (vi) atmospheric pollution, ventilation heating and lighting, (vii) water supplies, (viii) removal and treatment of waste matters (ix) sites and building construction, (x) public health law (England and Wales). In addition there are appendices on (i) atmospheric moisture, measurement of humidity vapour pressure tables (ii) physics calculations and tables of factors, weights and measures (iii) anthropometric measurements (iv) resolutions and rules of the General Medical Council. The section on personal hygiene is contributed by Dr G P Crowden.

In this latest edition the section on the prevention and control of disease has been considerably amended and now includes details of recent work on chemotherapy, venereal diseases, typhus and yellow fevers, epidemic infective hepatitis, and leptospirosis. An important addition to section (i) is a summary of the Government's proposals for a National Health Service. Emergency legislation passed since the outbreak of war is included where the author considers that such temporary legislation may become permanent.

The book, which is intended primarily for students, includes numerous references to the literature and an excellent index.

SOCIAL ASPECTS OF TUBERCULOSIS

by S Roodhouse Gloyne London, Faber and Faber Ltd, 1944
148 pages 8s 6d [£0 425]

Dr Roodhouse Gloyne, Pathologist to the London Chest Hospital, has made numerous contributions to the literature on tuberculosis, and his purpose in writing this book is to describe, for health visitors and others interested in the social aspects of tuberculosis, the problems arising from this disease as they affect the individual and the community. After tracing the development of man's knowledge of tuberculosis from the earliest times to the present, the book describes the growth of tuberculosis dispensaries, hospitals and sanatoria, and the work of the associated social services. The writer presents statistics showing the prevalence of the disease and the value of the various methods for estimating it. The causes of the decline in the tuberculosis mortality-rate during the past century are considered, and the factors responsible for the temporary war-time increase in incidence are discussed. The various anti-tuberculosis measures are briefly described and there is a chapter on human tuberculosis of bovine origin and its control. Schemes of after-care and rehabilitation are suggested. Except for a chapter on tuberculosis in non-immunized races, the book is confined to the social aspects of the disease as they concern Britain.

This is a splendid book, which now makes available a full review of an important sociological problem. There is a good bibliography of texts for further reading on every aspect of the subject. Such a good book as this deserves a better index. Chapter headings: (i) from consumption to tuberculosis, (ii) the tubercle bacillus, (iii) favourable and unfavourable soils for tuberculosis, (iv) classifications of tuberculosis, (v) the four ages of tuberculosis, (vi) human tuberculosis of bovine origin, (vii) infection and the portals of entry, (viii) the prevalence of tuberculosis, (ix) the decline of tuberculosis, (x) tuberculosis in non-immunized races, (xi) tuberculosis in industry, (xii) carriers and contacts, (xiii) case finding and prevention, (xiv) care and aftercare, (xv) tuberculosis legislation, (xvi) some conclusions.

ELECTROTHERAPY WITH THE DIRECT AND LOW FREQUENCY CURRENTS

by E B Clayton London, Baillière, Tindall and Cox, 1944 271 pages, 85 diagrams 10s 6d [£0 525]

The object of this book is to provide an account of the subject sufficient to cover the requirements of students working for part 1 of the Chartered Society of Physiotherapy examination in electrotherapy. The second part of this examination is already provided for by the author's *Actinotherapy and diathermy*, 1940.

The methods of production, effects and uses of faradic, sinusoidal and direct currents, together with the elementary physics required, form the main subjects discussed in the book. The numerous illustrations of the text greatly assist in explaining the use of apparatus and the actions of electricity.

The technique of treatments is explained, special mention being given to zinc and histamine ionizations. Muscle testing is described in detail and there is a full account of the normal reaction and of the reaction of degeneration. The two final chapters deal with the treatment of various disorders and injuries, including facial paralysis, Erb's palsy, cervical rib, nerve lesions of the limbs, neuritis, pressure paralysis, acute anterior poliomyelitis, progressive muscular atrophy, arthritis, fibrositis, etc.

PARODONTAL DISEASE

A Manual of Treatment and Atlas of Pathology

by E. W. Fish. London, Eyre and Spottiswoode (Publishers), Ltd, 1944 186 pages, 72 illustrations 18s 0d [£0 9]

The book sets out in a clear and concise manner the local surgical and chemical methods of treating parodontal disease which the author has found of value in his own practice. Gingivectomy, packing of gum pockets, tooth-pick friction, etc., are dealt with at length in a fairly orthodox manner and differ little from the procedures described by other clinicians. The text is amplified by numerous illustrations and diagrams, and the preferences of the author for particular instruments and techniques are explained. In addition, the need for sterilizing diseased gum around teeth requiring extraction in order to prevent bacteraemia is discussed at some length, this is based on earlier experimental work (Fish & Maclean, 1936).

The more theoretical aspects, relating to the aetiology, pathology and classification of the various forms of parodontal disease are less satisfactory. It is difficult to dissociate the empirical from the scientific, and hypotheses are often dogmatized as facts. The whole problem has been over-simplified to an extent that is in direct conflict with the experimentally-supported observations of many other workers. It is generally agreed that in most, if not all, lesions of the parodontal tissues local traumatic factors are important aetiological agencies. Dr Fish asserts that they are the only ones of any import. "The prevention of pyorrhoea is, therefore, the problem of keeping the surface of the gum margins hard from the earliest years of life. Treatment resolves itself into either devising a way of healing the ulcers at the bottom of the [gum] pockets and keeping the new epithelial lining of the pocket intact, or of obliterating the pockets, healing the wound so caused and thereafter keeping the epithelium of the new gum margin hard right up to its attachment to each tooth (pp 68, 69). According to the author, then, the only means whereby parodontal disease can be prevented involve the friction of the tooth-surface (by hard food

or by tooth-picks, etc.) irrespective of the original structure of the gum and of any systemic agencies which may subsequently alter it for better or for worse. The argument that "savages" (a needlessly uncomplimentary name for the primitive native) have remarkably healthy and horny gingivae due to the severe friction of the gum surface by the hard fibrous foods which they eat, would seem to be partly inaccurate and therefore irrelevant. It is well known that many primitive races, at one time at least, subsisted on food of such hardness that considerable attrition of the teeth occurred—and yet they showed evidence of severe gingival disease. He then goes on to say that for the "civilized" patient it is not worth while bothering with irksome changes in the consistency of the diet. "It is better to devise for him some artificial means of supplying the missing friction, which can be carefully graduated and accurately applied, just as he has discovered for himself an artificial means of increasing the nourishment value of his food but has had to have its vitamin content artificially restored to it." This is a strange analogy in view of the author's antagonistic attitude to anything related to nutrition. Nevertheless, if it is allowed that mechanical friction of the gum surface is one important factor in parodontal health, and this is highly probable, the use of graduated, artificial friction both for prevention and for treatment of disease is a method with which none can be in disagreement. But it is surely carrying the argument too far to suggest that sudden changes in hardness of the food were responsible for the outbreaks of "trench mouth" (Vincent's disease) seen in the last war. Enough work has been done, in the present war alone, to illustrate the fallacy of such reasoning.

Regarding systemic factors, the author remarks (in one small paragraph of 12 lines, p 34) that, while vitamin deficiencies "both A and C and even B" are cited as predisposing causes of parodontal disease, "both the clinical and histological pictures are different in these deficiency diseases. By all means let any deficiency in this direction which may be suspected be relieved, but the pyorrhoea will still remain to be dealt with and will not be improved. There is moreover no consensus of opinion that treatment by local surgical measures will even be aided by this kind of therapeutic support and the author has not found any case hitherto [including, apparently, Vincent's disease, see p 132] which failed to respond normally to efficient local measures without such administration." A vast amount of experimental and clinical investigation, to which not one reference is given, is thus dismissed as of no account (see King, 1944a). Indeed the only systemic factor which the author allows (p 34) is concerned with so-called pregnancy gingivitis and this, apparently, solely because Ziskin, Blackberg & Stout (1933) found thinning of the keratinous layer of the gum in such cases. Later, however (pp 59, 60), he discusses the difference in the gingival epithelium in "tough" or wiry men and delicate women. Such differences must surely be of systemic origin and so presumably affect the predisposition of the parodontal tissues to disease.

Turning to quite a different aspect, involving the explanation Dr Fish advances for the different colour changes in the gingivae as health gives way to disease (p 58), it is again difficult to discover the evidence upon which his dogmatic statements are founded. Indeed, in view of subsequent experimental work on the relationship between the epithelium and blood-vessels of the gum in health and disease (King, 1944b), such explanations are incompatible with the actual facts.

Two other peculiar points arise in reviewing this book. One, a minor one, relates to the author's apology for coining the term "odontoclasia" referring to resorption of tooth roots and sometimes of the surrounding bone (p 54). The term is no new one and has been in use, in America and elsewhere, for some years. The second point concerns his description of the action of tannic acid, copper sulphate, chromic acid, etc. as one of "tanning," since they cause precipitation or coagulation of tissue proteins (pp 69, 133). The usually accepted view of their action is that of destroying or burning away of the diseased surface tissue accompanied by vasoconstriction. Moreover, the process of "tanning" involves complete dehydration of the tissue—an impossibility in the mouth. Thirdly, Chapter x would seem to be redundant, its contents having been dealt with in detail in previous chapters.

Lastly, the "Atlas of Pathology" gives 26 well-produced plates intended to supply histological and other evidence in support of different statements made in various parts of the text. It is supplemented by descriptions of each plate, and little further comment is required here. It should be mentioned, however, that figs 50 and 51 (of rat's erupting molar teeth) give a somewhat misleading impression of the relationship of the enamel cuticle (Nasmyth's membrane) to the keratinous layer of the gum in man. In the human subject there is no "keratinous invagination" into the upper part of the gum corium as shown here. The cuticle is itself formed from the remnants of the enamel organ and, at eruption of the tooth, covers and is organically continuous with the whole of the enamel from the top of the tooth-cusp to the beginning of the cementum.

Chapter headings: (i) the nature and aetiology of parodontal disease, (ii) the dangers of parodontal disease, (iii) classification, clinical course and diagnosis of parodontal disease, (iv) methods of treatment and results, (v) individual case management and the systematic approach, (vi) instruments and their uses, (vii) the operation of gingivectomy, (viii) complications and difficulties, (ix) acute ulcerative stomatitis, (x) the relation of diagnosis to treatment, Atlas of pathology.

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One of the necessary consequences of the war has been an intensification of interest in local and systemic responses to physical injury. While there have been great improvements in the treatment of the injured, these have been largely due to technical advances in such collateral fields as chemotherapy and the infusion of blood and its derivatives. Improvements in transport and organization have also played a part, particularly in certain special types of injury.

In this number of the *Bulletin*, an attempt has been made to present some of the fundamental considerations underlying the related clinical problems of wounds, burns, and "shock". It will be clear from the contributions to this number that exact knowledge of the mechanisms of reaction to injury is still far from complete, and that, on some important questions, there is disagreement not only in detail but in principle. However, the diversity of the special branches of biological and medical science represented by the authors of the contributions testifies to the complexity of some of the problems and strengthens the case for collecting their views in a single number of this *Bulletin* on "Injury and Repair".

MR. P. B. MEDAWAR, who contributes two articles in this number, is a Fellow of St. John's College, Oxford, and a University lecturer in zoology. He has worked at Oxford since graduation there in 1935. In peace-time his interests lay in the mathematical interpretation of growth and change of form during development. After spending a year as a member of the Oxford team (whose work was described in Vol. 1, No. 7 of this *Bulletin*) studying the repair of injuries to nerves, during which he introduced the technique of fibrin suture into surgery, he turned to the study of skin grafting. He is developing this study, not only on the theoretical side, in relation to the biology of individuality, but also with reference to its clinical applications.

DR. J. N. DAVIDSON took degrees in chemistry and in medicine at Edinburgh University and later went abroad to engage in research in biochemistry under Professor Otto Warburg. Returning to Britain in 1938, he was appointed lecturer in biochemistry in the University of St. Andrews at University College, Dundee. Since 1940 he has been lecturer in biochemistry in the University of Aberdeen. Dr. Davidson has worked on the metabolism of fructose, on the purification of enzymes, and on the absorption of substances from the intestine. During the last few years he has been engaged in research, with the assistance of Dr. C. Waymouth, on the biochemical aspects of the problem of tissue growth and its relationship to wound-healing. This work has laid special emphasis on the ribonucleic acids of the cell cytoplasm, and has formed a link with discoveries which have been made in related fields in the United States and in Sweden.

DR. G. H. BELL is at present a senior lecturer in the Institute of Physiology at Glasgow University. He has carried out research work in various laboratories in Britain and in Germany, and was for a short-time lecturer in Bristol University. His early work was mainly concerned with reproductive physiology, with especial reference to the hormonal control of uterine activity. He has designed a simple form of photoelectric absorptiometer for examining the various procedures used in the estimation of haemoglobin. More recently he has been investigating the influence of nutrition on the chemical and physical properties of bone.

PROFESSOR R. A. PETERS was educated at Cambridge University and St. Bartholomew's Hospital, London, and was a pupil both of Sir Joseph Barcroft and Sir F. Gowland Hopkins. During the war of 1914-18, he spent 9 months as a battalion medical officer, and was awarded the M.C. (with bar), but was recalled for scientific work. In 1923, Peters left Cambridge, where he was Dunn lecturer in biochemistry, and became Whitley professor of biochemistry and a Fellow of Trinity College, Oxford. After early work with Barcroft on the specific oxygen capacity of haemoglobin, he turned his attention to vitamin problems, and his name is particularly associated with work on the vitamin-B complex. In 1930 came the first demonstration of the *in vitro* action of a vitamin—the specific response of avitaminous pigeon's brain to vitamin B₁. This led to proof of the intimate connection of this vitamin with the metabolism of pyruvic acid. During the present war Peters, while maintaining his interest in nutritional problems, has directed two teams of research workers on specific war problems. One of these teams has been engaged on work for the Ministry of Supply, and the other has been working on burns for the Medical Research Council. The work on burns is described by Peters in his article in this number of the *Bulletin*.

PROFESSOR G. R. CAMERON studied medicine at Melbourne, Australia, and Freiburg. He was assistant director of the Walter

and Eliza Hall Institute, Melbourne, Australia, before being appointed to University College Hospital Medical School, London, as assistant to the late Professor A. E. Boycott, whom he succeeded as professor of morbid anatomy in the University of London. Cameron's interests have been chiefly experimental and he has given most of his time to studies on fundamental tissue-responses to injury, especially in the case of the liver. In latter years he has been concerned in a number of toxicological investigations associated with the introduction of new insecticides and drugs. During the present war he has also been concerned in the study of the pathology of thermal and chemical burns.

DR. F. H. K. GREEN has been a member of the administrative staff of the Medical Research Council since 1929, and is the Council's publications officer. In the latter capacity he is responsible for the editing of the Council's Special Reports and War Memoranda, and shares with the staff of the Bureau of Hygiene and Tropical Diseases the task of producing the *Bulletin of War Medicine*. Since 1940 he has also been secretary of the War Wounds Committee and of most of its sub-committees, including that on burns. In this capacity he has been closely informed of all important British work on burns and their treatment during the past 5 years.

DR. D. P. CUTHBERTSON was the subject of a note in an earlier number of the *Bulletin* (Vol. 2, No. 10-11). It remains to be said that he has given very useful advice in the planning of this number.

PROFESSOR H. N. GREEN holds the chair of pathology at the University of Sheffield. He has worked in a wide field of experimental medicine, aiming throughout at a close liaison between the laboratory and the ward. His early researches in the laboratories of Sir Edward Mellanby at Sheffield were mainly concerned with nutrition, and he published a variety of papers dealing with diet and infection, diet and pregnancy, and the biochemistry of vitamins A and D. Later he became a demonstrator at the University of Cambridge and there, whilst working on bactericidal factors in the blood, became interested in chemotherapy. He has contributed in several papers to our understanding of the mode of action of sulphonamides and related compounds. During the war he was asked by the Medical Research Council to organize a clinical team to study traumatic shock. These investigations led to pure laboratory studies in which the shock-inducing action of adenosine triphosphate was discovered. This work is reviewed in his article in this number of the *Bulletin*. More recently Green has commanded the British Traumatic Shock Team, 2, R.A.M.C., and has directed investigations in battle zones in NW Europe. He is director of the Sheffield Cancer Research Laboratory and summaries of his investigations are to be found in the annual reports of the British Empire Cancer Campaign from 1937 to 1945. He is also director of the Sheffield Blood Transfusion Unit.

DR. J. McMICHAEL is reader in medicine in the University of London, and since 1939 has been acting director of the department of medicine in the British Postgraduate Medical School. His earlier work was done in the Universities of Edinburgh and Aberdeen and also at University College, London. His first contributions dealt with diseases of the liver and spleen (with J. W. McNee), studied with special emphasis on the physiology of the portal circulation. He then began research on heart failure and has been concerned with cardiac-output studies in man since 1936. He also developed techniques and methods for the study of respiratory problems in man. In his department during the war, McMichael has been ably assisted by Dr. E. P. Sharpey-Schafer in studies on haemorrhage, Dr. E. G. L. Bywaters on crushing injuries, and Dr. Sheila Sherlock on biopsy studies on hepatitis. He is a strong advocate of the direct application of physiological methods to the problems of human disease.

DR. E. G. L. BYWATERS at the beginning of the war was a Beit Fellow working at the British Postgraduate Medical School on metabolic changes in rheumatoid arthritis. He had previously studied the physiology and pathology of joint-tissues at the Courtauld Institute of Biochemistry as McKenzie McKinnon research Fellow, and with Dr. Walter Barrow at the Massachusetts General Hospital as a Rockefeller travelling Fellow. When the aerial bombardment of London started, he joined the Hammersmith team doing work on 'shock', and studied cases of crush syndrome, later forming one of a mobile team for this purpose. He recently spent a year as deputy director of the Medical Research Council Unit at the Royal Victoria Infirmary, Newcastle-upon-Tyne, investigating biochemical aspects of industrial and traffic accidents. His published work includes papers on crushing injury—clinical, experimental and pathological—and on aspects of joint physiology.

REVIEW OF SELECTED PAPERS. Contributions to this section have been received from Professor J. H. Dible, Dr. A. Glucksmann, Dr. F. Hawking, Dr. E. Lewis-Fanning, Mr. P. B. Medawar, Mr. D. H. Patey, Dr. G. Popják, Professor Arnold Sorsby and Dr. R. Wyburn Mason.

BIOLOGICAL ASPECTS OF THE REPAIR PROCESS

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The biologist very often makes a distinction between "regeneration" and "repair"—or, more emphatically, between "true regeneration" and "mere repair". It is the scale rather than the quality of the difference between them that the biologist has in mind, for it is not true that regeneration alone of the two involves a process of form-determination. Like many another distinction which has a long history of intelligible use, it is not made sharper by close inspection, nor less useful for the want of it.

Although regeneration in general has never been made the subject of a really systematic investigation by biologists, some attempt to present the outcome of their researches to a medical audience is long overdue. In what follows, the writer has tried to deal in moderate detail with two topics that have a more or less direct bearing on the theory of wound healing, and in sketchy outline with two others of a more purely biological nature. To avoid weighing down the text with references, review articles have so far as possible been quoted in place of original sources.

The state towards which the repair process tends—its "final cause", Aristotle would have called it—is the restoration of the *status quo ante*. How the subordinate processes are so interwoven one with another that they do achieve this end, and having reached it stop, is an almost complete mystery. The terminology which many biologists adopt, of "fields", "gradients" and the like, gives the impression of an understanding of these processes which has in no single instance been achieved. No useful purpose would at present be served by defining and criticizing these *ad hoc* theoretical constructions. Some discussion of the matter is given by Huxley & de Beer (1934, pp. 271–301), their treatment has been criticized by Needham (1942) (See also Weiss, 1939, Child, 1941).

Cellular "Kinetics" and the Repair Process

The title of this subsection might once have seemed pretentious and affected. To-day, it can be given a surprisingly literal meaning. The *tactics* of regeneration, as of embryonic development, is primarily and fundamentally a matter of the movement of cell-substance, cells, and cell groups. It is not primarily a matter of cell-division nor of synthesis in general, though in due course these are called upon to play their part. Evidence for this generalization may be taken first of all from the field of embryonic development.

It is characteristic of vertebrate development that after a period of cell-division—"cleavage"—which serves amongst other things to increase the nucleo-cytoplasmic ratio and to make a mechanical subdivision of the embryo into physically workable parts, the cells of the embryo come to be arranged into a simple or stratified epithelial sheet. The strategical objective of early development, viz. the establishment of the embryonic axis in the process of gastrulation, is secured by the generalized and local foldings, stretchings and convolutions of the epithelial sheet and the subordinate germ layers which develop in physical continuity from it. The words used in up-to-date accounts to describe these processes are "flow", "streaming", "migration", "pull", "folding", "displacement", and so on. Vogt (1923), to whom above all we owe this kinetic picture of development (see Spemann, 1938) writes "There is, strictly speaking, but one expression for the kind of process we have before us, 'amoeboid motion', not, however, of cells but of the whole gastrula or rather of its parts in the course of their development." It is not, as His (1874) believed and many biologists still do, high rates of cell-division locally nor the cell-division pressure that might result from it, that make the tactics of early development. The best evidence (Pasteels, 1934, 1936, Holtfreter, 1943, Gillette, 1944) is that, although cell numbers do increase in the course of gastrulation, the rate of increase is fairly uniform throughout the embryo. The same is true, of the beginnings of organ formation

The majority of organs begin as evaginations or inrollings of a tube or sheet: liver, lungs and pancreas from the archenteron, optic cup from the brain vesicle, nerve tube from the medullary plate, and so on. Indeed, the anatomical classification of the glandular organs makes use of the manner of their derivation from epithelial sheets (Clark, 1939). Nature, as Oliver Wendell Holmes expressed it, works like a glass-blower—an analogy which becomes progressively more apt as the years go by.

These generalizations have an immediate relevance to the repair processes. Exactly the same principles underlie the closure of epithelial defects by secondary healing. "The chief biological factor responsible for the extension of epithelium over [a] denuded area is the amoeboid movement of the neighbouring cells themselves" (Arey, 1936). Cell-division and synthesis step in later to make good the loss of mere substance, but the shaping-and-forming element of the repair process is kinetic and not synthetic. Arey's review (1936) of the kinetics of epithelial healing is definitive (see also Leslie-Roberts, 1941). The most decisive of the more recent demonstrations of the fundamental role played by the mass migration of epithelial sheets are those of Arey (1932) and Herrick (1932) on epidermal healing in fishes and amphibia, of Arey & Covode (1943) and Mann (1944) on the healing of the mammalian cornea and of Wigglesworth (1937) on the repair of insect cuticle. (In corneal healing there is actually a drop in the rate of cell-division during the migration period.)

Thus students of wound healing on the one hand and embryologists on the other are working independently but in parallel to give precision to a single general principle. It has long been known, moreover (cf. Holmes, 1914), that the spectacular deployment of epithelia from cultured tissues is another instance of the "amoeboid movement" of cell sheets, and that cell-division plays no significant part in their lateral displacement. Wilbur & Chambers (1942) have made a particular study of the healing of micro-wounds in cultured epithelial sheets, and describe the formation of undulating membranous processes on the individual cell in anticipation of its movement. Cell-division plays no part in the healing of such wounds. There is no space here to deal with many kindred phenomena, such as the streaming movements of slime moulds, save to point out that they will no doubt in the long run take their place in a single comprehensive scheme of tissue kinetics. Special mention must nevertheless be made of the mechanism of bud-formation in Tunicates (see Berrill, 1945), for here too the same general principles of epithelial folding and convolution are exemplified.

The role of cell movement in repair is not confined to, nor even best demonstrated by, the epithelia. The invasion and subsequent "organization" of clot by fibroblasts and endothelial cells, the passage of leucocytes through vessel walls, and so on, are primary matters of cellular movement—so well known that their wider significance has been forgotten or overlooked. Particularly striking confirmation comes from the study of regenerating nerve-fibres. Cell-division can be eliminated, as adult nerve-cells do not divide, and the parts played by synthesis and the movement of cell-substance can be dissociated. Harrison (1910) and Speddel (1933) showed that the regenerating axon tip behaves in the manner that was called "amoeboid" long before the particular analysis of movement in *Amoeba* itself gave that word the more limited significance that it may have to-day. Young (1944, 1945), goes farther: the regenerating nerve-fibre is produced by the outward streaming or flow of the central part of the axon protoplasm as a whole. Nor is the process accompanied in the first instance by synthesis, i.e. by manufacture of new axon substance, for Gutmann & Sanders (1943) and Sanders (1945) find that the cross-sectional area of the fibres in the central stump of a divided nerve falls off

in just the manner that would be expected from a process of attenuation unaccompanied by increase in bulk.

An extension of similar principles to the interpretation of the repair of *muscle* fibres is to be expected in the near future, for in preliminary work Clark & Blomfield (1945) already find evidence of the "streaming of nucleated strands of protoplasm" from the stumps of damaged fibres.

The significance of the foregoing generalizations for the theory of wound healing is fairly clear. All attempts to guide and to accelerate the healing process have hitherto taken the form of a search for stimulants of cell proliferation and protein synthesis. It is by no means certain that such a stimulant is either necessary or desirable—at least for the critical early stages of healing. What is needed is a precise formulation of the kinetics and mechanics of healing, such as Weiss (1944) and Young (1944, 1945) are beginning to make for the primary union of divided nerve. The more difficult task of attempting to facilitate, guide and stimulate the cellular and cytoplasmic movements of repair will then have an adequate theoretical foundation. An analysis of the all-pervasive mechanism of "amoeboid movement" in epithelial sheets is a matter of even greater urgency and importance. A very tentative beginning has been made with the work of Waddington (1939) and Holtfreter (1944), but this is concerned, unfortunately from our point of view, not with the mechanism of epithelial spread in general, but with the very complicated and special form that it takes in the movements of gastrulation.

The Tempo of the Repair Process

The repair process is preceded by (or includes as its first stage) a latent period within the compass of which healing is either inappreciable or functionally ineffective. The analysis of the latent period is a complex matter, since it may have a widely different significance in each of its instances, and since regeneration is in any case the integrated sum of a number of subordinate processes which, although they do in fact work together, are usually dissociated by the investigator. The "scar delay" in divided and sutured nerves of the rabbit, i.e. the period of retrograde changes in the central stump which precedes the outflow of axoplasm, is about 7 days (Gutmann, Guttman, Medawar & Young, 1942). The latent period before the migratory activity of the Schwann cells begins is about 3–4 days (Weiss & Tahlor, 1943), or 5–6 days as determined by transformed measurements *in vitro* (Abercrombie & Johnson, 1942).

In the healing of incisions which traverse the dermal layer of skin, the latent period represents the time that is necessary for newly-formed collagen fibres to knit the skin-edges together in a union of adequate mechanical strength. An appropriate criterion of repair is, in this case, the resistance of the line of union to rupture. The pioneer investigations of Howes, Sooy & Harvey (1929) gave 4–6 days as the length of the latent period before tensile strength begins to increase, more recent investigations on the same lines have served to establish the superiority of silk to catgut sutures (Localio, Casale & Hinton, 1943). In general, then, the nature and length of the latent period can be specified only with regard to some chosen criterion of repair, and it does not lend itself to the making of broad generalizations. It is a safe guess, however, that migratory activities always anticipate those of cell-division. The latent period before the former begins may indeed be negligible (cf. Arey & Covode, 1943).

Once the repair process has started, its rate conforms with that of organic growth processes in general, i.e. the specific rate¹ falls off as the process of repair moves towards completion (cf. Medawar, 1941). Sometimes the rate itself falls off progressively, so that the curve of repair is uninflected. Otherwise, there is a period of increasing rate followed, at a time-level defined by the point of inflexion, by a period of decrease (see the data and discussion of Thompson, 1942 and of Abeloos, 1932). In any event, attempts to fit exact, non-empirical, algebraic equations to the curves of repair are quite futile: any set of data defines a whole class of possible choices, and no significance can be read into the fact that, in a particular instance, one may be better than another (Seddon, Medawar & Smith, 1943).

Nevertheless, the general shape of the curve of repair

¹ [The specific rate is the quotient of the rate at some chosen time by the amount regenerated at that time, i.e. dx/dt instead of dx/dt , where x represents the amount in question]

(there is nothing vague or imprecise in such a concept: the shape may be defined by the analytical properties of the derived functions) contains information of importance. Any prognosis of functional recovery after nerve lesions should for example take into account the fact that its rate of attainment will be slower latterly than it was in the earlier stages (Seddon *et al.*, 1943). The analysis of the rates of regeneration of nerve (Gutmann *et al.*, 1942) illustrates very clearly how completely dependent is the concept of a "rate of repair" upon the nature of the criteria by which the investigator chooses to measure it. The general shape of the curve of repair, like that of the curve of growth, is that of a system moving towards a state of equilibrium. Robertson (1923) based his growth formulae upon the rather too literal assimilation of organic growth to the movement of chemical systems towards equilibrium.

The best-known attempts to define by formulae the rate of healing of skin defects are those of du Noüy (cf. 1936), others are discussed by Arey (1936). No particular one has found universal acceptance, nor is the need for any formula widely admitted. In certain cases, however, the surgeon may come to admit the slide-rule as a minor instrument of prognosis, but that will not be until data have been amassed of greater weight and higher precision than hitherto.

A Note on the Natural History of Regenerative Power

The phenomena of regeneration, asexual reproduction, and (uniovular, "identical", or monozygotic) twinning are closely related to each other—the first and second in adult life, and the first and third at its very beginnings. On the basis of such evidence as that summarized by Abeloos (1932) or Korschelt (1927), which needs correction and amplification in several particulars, one may demonstrate an almost faultless correlation between the capacity for asexual reproduction and the power of an organism to regenerate itself in full from some fragment lacking the head or (as that term is not very precise) what is commonly called the head-end or anterior end. In some animals—marine worms of the class Polychaeta, and certain species of Enteropneusta, distant relatives of the starfishes and sea-urchins—parts of the hind-end break off repeatedly and in due course develop into whole new organisms. The somewhat adventitious occurrence of this method of reproduction among the families of the class, and its obvious association with the type of injury that a worm-like animal would most commonly receive, suggest that in these cases a capacity for regeneration has anticipated and, in a sense, evolved into a mechanism of asexual reproduction. In animals which reproduce by budding (of which the Tunicates, sea-squirts, are the best examples) no such priority can be allotted. (It has already been pointed out that in these forms the bud develops by the folding, convolution and amplification of the two layers of an epithelial primordium, by a series of typical "morphogenetic movements", in fact.) The powers of asexual reproduction and regeneration are, it may be noted, very capriciously distributed not only among the classes of a phylum—among worms, for example, the leeches lack them—but even among the species of a single genus. With this qualification in mind, one may nevertheless demonstrate a general decline in both faculties through the evolutionary series. The most highly organized animal to reproduce asexually in the adult form is the starfish. Its dramatic powers of regeneration are well known. There are, of course, inexplicable anomalies. The Nematodes and Rotifers have very little regenerative power. From their general level of organization we should expect them to have some power of asexual reproduction, but we find curious variants of sexual reproduction instead: alternation of generations between hermaphrodite and dioecious forms in Nematodes, and parthenogenesis in Rotifers. The correlation between regenerative power and asexual reproduction therefore remains exact.

Entirely different problems are raised when one turns from adult to embryonic animals. The power of asexual reproduction is here represented by monozygotic twinning, and this is in turn exactly correlated with a variant form of regeneration, namely the power of a single daughter-cell of the zygote to develop, in isolation from the others into a whole organism. It is not an affectation to speak of monozygotic twinning as asexual reproduction, for even in one mammal, the nine-banded armadillo (cf. Newman, 1942) its occurrence is regular and not a matter of chance.

The power of daughter cells of the zygote to reproduce the whole is called the power of *regulation*. It is just as variously distributed among the members of a group as the power of asexual reproduction. The, at one time, grand distinction between the phyla or classes which do or do not possess "regulation eggs" is therefore no longer thought to be particularly significant (see Needham, 1936, Dalcq, 1938). But it is noteworthy that the power of eggs to "regulate" is in no way correlated with the power of the adult either to reproduce asexually or to regenerate the whole from a part lacking the head or oral end. The Tunicates have non-regulative eggs, for example, but have the most remarkable powers of asexual reproduction and regeneration. Man shows identical twinning, i.e. has a regulation egg, but lacks any dramatic power of regeneration in the adult.

The power of regeneration might well be thought to decline continuously throughout life. This is not so. The newts, for example, begin life with regulation eggs and the power of twinning, and end it with very extensive powers of regeneration. But during an intermediate period, very near the beginning of development in point of time but far removed from it in point of developmental complexity, the power of regeneration is in abeyance. This is the period during which the primordia of the organs first become recognizable as buds or as topographically defined territories, when regional differentiation, in fact, begins to take over from the central or systemic organizing influences which have resulted in the formation of the embryonic axis. The extirpation of an organ-rudiment at this so-called "mosaic stage" (cf. Huxley & de Beer, 1934, pp. 194-270) cannot be made good: the adult will lack the organ, even if it could itself have regenerated it. *Amblystoma*, for example, can regenerate a leg, but it develops without one if the organ-rudiment has been removed from the embryo (Harrison, 1915). Localized trauma or extirpation of the parts of an organ-rudiment produces specific localized defects or abnormalities in the adult organ: if the adult organ is then removed, that which regenerates in its place faithfully reproduces the defects of the original (Vogt, 1931). "It appears in these cases that the organism cannot regenerate a structure which has never been formed in its own [development]." The more one thinks of this phenomenon in terms of the actual mechanism of regeneration, the more remarkable it becomes.

This brief sketch of the natural history of regenerative power may serve to put the repair processes of the human being in that wider perspective in which alone they can be properly understood. Its more immediate bearing on the phenomena of twinning and of human teratology has been discussed by Newman (1942) and Needham (1942) respectively.

Cellular Inheritance and Repair

In almost all the cases of repair with which the surgeon deals, the new cells which are manufactured in the course of healing are lineal descendants of cells of the same histological type. Fibroblasts, epithelia, endothelial cells, and so on, are not differentiated *de novo*, but are derived from fibroblasts, epithelia and endothelia from the bed and margins of the wound. It is far otherwise with the radical regeneration of (say) the newt's limb, for this is accompanied by "morphogenesis" in the embryological sense, i.e. by progressive irreversible differentiation within a rudiment or primordium—the regeneration bud—in which the cell-types later to emerge are not yet recognizable as such. In both cases a problem of cellular inheritance arises, but in the former it is not complicated by inheritance accompanied by progressive cellular modification. We have only to consider how it is that the descendants of a somatic cell retain for an indefinite period its specificity of histological type—of gross and fine structure, metabolism, and behaviour. For of the empirical fact there can be no doubt: even cells cultured through hundreds of cellular generations *in vitro* retain their specificity of type, or depart from it only by the minor, temporary and reversible changes which Weiss (1939) has so aptly called "modulations." In formal terms, the problem is of the nature of inheritance in cells related to each other by mitotic descent. The problem is by no means confined to, but is best exemplified by, the phenomena of regeneration and experimentation. This section is intended to contain a brief statement of the problem, with a number of references to such of the recent literature as is relevant to it.

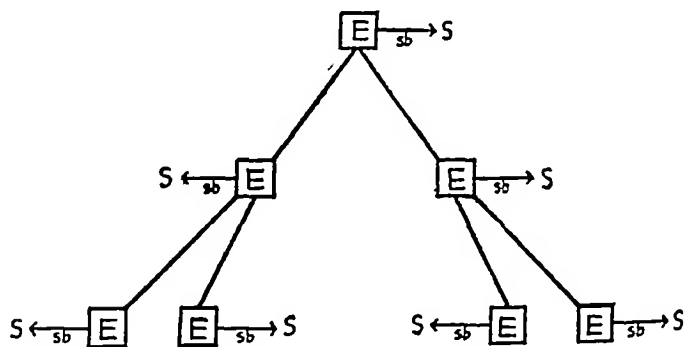
It may at once be said that the passive transfer of cytoplasmic substance from parent to daughter cells is not an

adequate explanation of cellular inheritance. It is true that the cytoplasm of the parent cell is shared between its daughters and that if it had been stained with (say) neutral red, the daughter cells would inherit its coloration. But the colour would become progressively feebler, and that is just what does *not* happen in cellular inheritance. Indeed, one can easily reduce such a hypothesis to absurdity: there must come a time when the parent cell has but one dye molecule to share between its daughters.

Are the nuclear genes responsible for cellular inheritance as well as for inheritance by or through the germ-cells? Indirectly, they must be, but it is not likely that nuclear genes are the physical instruments by means of which the determinants of a cell's character make-up are distributed at cell-division. According to the fundamental theorem of experimental embryology (cf. Needham, 1936, Spemann, 1938), *all* the cells of the individual have the *same* complement of nuclear genes. (It seems almost impossible to believe that the same genes come into physical operation in cells of all histological types—but that qualification is taken into account below.)

In a preliminary approach to the problem, it is helpful to concentrate upon a single instance of cellular inheritance—say upon the inherited power of thyroid epithelium to produce its characteristic secretion. For the sake of simplicity we may suppose that only one enzyme is concerned in making it. The fact that there must be several does not invalidate the argument.

The manufacture of its typical secretion is part of the inherited character make-up of the thyroid cell, just as much so as its gross and fine structure and its staining reactions. The power to produce the secretion is inherited indefinitely, so that the enzyme(s) concerned must be repeatedly manufactured anew. The enzyme, or the particle or micelle which carries it or has enzymic activity, has therefore two duties to perform: it must manufacture its specific secretion in the presence of the appropriate substrate, and it must also reproduce itself. The self-reproduction may be, as it were, a side-line of the enzyme or enzyme-carrier's activity, but something is gained in clarity by supposing that self-reproduction is the "main" function and ordinary enzymic activity a subsidiary one. The accompanying sketch represents the postulated scheme of enzyme reproduction. The letter E stands for "Enzyme"—it is enclosed within a box to indicate that the faculty of reproduction may belong to the micelle on which the enzyme is carried. The letter S stands for "Secretion" or enzyme-product, and the abbreviation sb for the enzyme-substrate.



The diagram as it stands suggests that the enzyme reproduces itself amoeba-wise, by fission, as mitochondria do, but it is just as likely to be by process akin to carbon-copying, with or without a negative "master" between the positive original and its positive reproduction (see Haldane, 1937).

As soon as a scheme such as this one is produced and figured, one begins to think of *genes*, and with some justice, since the enzyme is behaving like a gene in securing the inheritance of an aspect of the cell's character make-up, and like a gene also in the way it reproduces itself. For the reasons already given, we locate this enzyme-gene in the cytoplasm rather than in the nucleus. It may earlier have migrated from the nucleolus or it may be a modified reproduction of a nuclear gene itself (cf. Waddington, 1940). Neither possibility is inconsistent with the hypothesis.

Do cytoplasmic genes exist? Evidence from a variety of different sources (Darlington, 1939, 1944, cf. Haddow, 1944), not collected with the special problem of inheritance in adult somatic cells in mind, suggests very strongly that they do. Indeed, certain cases of inheritance which are anomalies from the Mendelian point of view, such as the inheritance by

strains of *Paramecium* of the power of poisoning their culture-media for paramecia of other strains, can be explained only by supposing that genes are carried in the cytoplasm—are *plasmagenes* as Darlington has called them. In some cases the carrier of the cytoplasmic gene may be as well-defined physically as the chromosome which carries the nuclear genes. Such is the case with green plastids in plants, which reproduce by fission: a mutant plastid, white instead of green, will transmit the white character to the daughter cells into which it passes. The inheritance of the variant form is independent of the nucleus, though the inception of the variant character may not be. Plant plastids clearly make a special case.

Can anything more general be said about the physical instruments of cellular inheritance? They are likely to be bodies largely composed of nucleoprotein, characteristically associated with self-reproducing systems (cf Davidson & Waymouth, 1944). Claude (1943), to whom we are indebted

for a particularly clear formulation of the problem of cellular inheritance, believes that the *microsomes* of the cell, described and identified in his laboratory, carry the determinants of cellular heredity: they are ribo-nucleoprotein bodies, 50–200 m μ in size and making perhaps as much as 10–15% of the dry weight of the cell. If his guess is correct, the microsome may prove to be the most important discovery in cytology since the behaviour of chromosomes was first associated with the behaviour of the genetic factors.

The mysterious problem of inheritance in cells related to each other by mitotic descent, fundamental to any complete understanding of the repair process, has now, therefore, the rudiments of a solution. Nothing need be said here of its wider implications for medicine: for the theory of the origin of viruses, to take one example, or for carcinogenesis. That they will in due course have a profound significance for medicine is a matter that can now hardly be doubted.

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HUMORAL ASPECTS OF WOUND-HEALING

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The healing of a clean incised wound may be divided into three main phases (Localio, Casale & Hinton, 1943): (i) The phase of traumatic inflammation, in which hyperaemia and exudation occur; (ii) the phase of destruction, in which the wound is freed of dead and dying cellular elements. These two phases constitute the lag period; (iii) the phase of proliferation, in which fibrous-tissue formation, contraction, and epidermization may occur.

The discussion which follows concerns mainly the third phase.

Effect of Nitrogenous Substances

The part played by protein and amino-acids in relation to wound healing has been reviewed recently by Cuthbertson (1944). As the result of wounding, nitrogenous material may be lost from three main sources: (a) Some tissue is destroyed at the site of injury; (b) protein is lost in the blood and serum from the wound. The amount of protein lost in the plasma of the exudate in cases of burning may be very considerable (Co Tui, Wright, Mulholland, Barcham &

Breed, 1944); (c) following the injury, there is a considerable loss of nitrogenous material in the urine (Cuthbertson, 1929, 1930, 1936, 1942) and this material is not derived merely from the area of injury.

It will be obvious therefore, that, after wounding, protein will be required in the diet in abundance to make good these losses,¹ and to supply the requirements of proliferating cells which are building up new tissue. Harvey & Howes (1930) have shown that although the feeding of a high-protein diet did not reduce the lag period in the healing of experimental wounds, it did accelerate fibroplasia in the third phase.

Effect of Hydrogen-ion Concentration

In any wound areas of local acidity may result from stasis and carbon-dioxide accumulation, or from the production of organic acids by cells suffering from oxygen-want. Various observers e.g. Girgolaiff (1924), Rohde (1927), Fontaine &

¹ [This subject is discussed in a paper by Dr D. P. Cuthbertson (BMB 691)—Ed.]

Jung (1928), Schade & Claussen (1926), and Messer & McClellan (1935) have measured the pH values of healing wounds, and found that they varied over a very wide range. There is little agreement as to the values required for optimum healing. A shortening of the period required for wound-healing, in dogs with acidosis produced by ammonium-chloride administration, is reported by Reimers & Winkler (1933), but Sandblom (1944) found that such acidosis had no definite influence on wound-healing, although it caused an unduly high incidence of stitch-abscesses. Robinson (1940) observed that alkaline solutions (e.g. ammonium carbonate, pH 7.7) promoted wound-healing and reduced the number of stitch-abscesses.

Effect of Vitamins

Vitamin C It has been recognized since the days of Lind (1772) that wounds are slow to heal in patients with scurvy, and this early observation is amply supported by recent work. Wolbach & Howe (1926) and Wolbach (1933, 1937) have concluded that, in scurvy, the cells fail to produce intercellular substance, and that this failure of collagen-formation can be corrected by administration of ascorbic acid (vitamin C). Deficiency of collagen-formation was observed by Hunt (1941) in the healing wounds of guinea-pigs partially deficient in ascorbic acid, and the process of healing was profoundly disturbed. In a series of wounds in human cases studied *post mortem*, poorest collagen-production was observed in those most deficient in ascorbic acid.

Lack of tensile strength in the healing of skin wounds in guinea-pigs deficient in ascorbic acid was correlated by Bourne (1944b) with a retardation in the substitution of collagenous for reticulin fibres. Crandon, Lund & Dill (1940) showed that an experimental wound could heal normally in a human subject who had subsisted for three months on a diet free from ascorbic acid, but after six months, when clinical scurvy was apparent, wound-healing was impaired.

In an extensive series of investigations on the healing of bone, Bourne (1942a, 1942b, 1942c, 1943, 1944a) has shown that the formation of the organic matrix, and probably also the deposition of calcium in the matrix, depends on an adequate supply of ascorbic acid. In its absence, the activity of both endosteum and periosteum in the repair process is diminished.

Administration of ascorbic acid to patients recovering from operations is accordingly recommended by Hunt (1941), Crandon, Lund & Dill (1940), and Bourne (1942c). Campbell & Cook (1942) have reported that large doses of ascorbic acid are of value in promoting the healing of tooth-extraction wounds.²

Vitamins A and D Vitamin D does not appear to improve the healing of wounds (Saitta, 1930; Lauber, 1933b, 1934), but administration of vitamin A in moderate doses is reported to have a beneficial effect (Lauber, 1933a; Lauber & Rocholl, 1935; Escarras & Paillas, 1938). Cod-liver oil, which contains both vitamin A and vitamin D, was first employed by Löhr (1934) as a dressing for wounds, and has been used by many other investigators. Its action in wound-healing was thoroughly examined by Dann, Glücksmann & Tansley (1942), along with that of other oils. They found that cod-liver oil, pure vitamin A, arachis oil, linoleic acid, coconut oil and liquid paraffin all stimulated collagen regeneration to varying degrees, but that epithelial regeneration was promoted by linoleic acid only.

Vitamin P This vitamin appears to play no part in wound healing (Hartzell & Stone, 1942).

Effect of Hormones

a Pituitary gland Hypophysectomy does not seriously interfere with the proliferation of fibroblasts and epithelial cells in wound-healing (cf. Seyle, Mortimer, Thomson & Collip, 1934), and administration of extracts of the anterior lobe of the pituitary gland has been shown to exert no significant effect on the healing time (as measured by reduction in area) of superficial wounds in rats (Cuthbertson, Shaw & Young, 1941). Such an extract does not appreciably stimulate the growth of fibroblasts *in vitro* (Davidson & Waymouth, 1943) but it is able to prevent the loss of body-weight, and the loss of nitrogenous material in the urine,

which follow fracture of the femur in rats (Cuthbertson *et al.*, 1941).

b Thyroid gland Thyroid-administration has been reported to be of value clinically in wound-healing (Lauber, 1930), and to cause acceleration of the healing of experimental wounds in animals (Kosdoba, 1934). Barclay, Cuthbertson & Isaacs (1944), investigating the healing of skin-wounds in rats, found a significant reduction (11%) in the mean time required for healing when dried thyroid gland was fed during the period of healing. If the animals were, in addition, given thyroid in the diet before operation, the time required for healing could be reduced by as much as 22%. A reduction in healing time (of 15–27%) could also be produced by feeding 2,4-dinitrophenol as a component of the diet in small doses (0.012%), but not in larger doses (0.09%). The authors do not, however, advise the use of these metabolic stimulants to influence the rate of normally healing wounds in human patients.

c Steroid hormones It has been suggested by investigators in America and in Canada that the adrenal cortex produces two hormones which are present in the urine in increased amounts in the first 24 hours after injury (cf. Cope, Nathanson, Rourke & Wilson, 1943). One, the "N" hormone, is a testosterone-like substance which causes retention of nitrogen. The other is termed the "S" hormone and causes conversion of protein to sugar, and therefore a loss of nitrogen. After trauma, the adrenal cortex first puts out an excess of both "N" and "S" hormones, which appear in the urine, but later only the "S" hormone appears in excess. Subsequently the output of "N" hormone diminishes also. At this stage, administration of testosterone might perhaps be expected to be of some benefit. The effect of local applications of testosterone on the healing of wounds in man (skin-graft donor-areas) has, however, been examined by Baxter, Stevenson, Schenker & Browne (1944). They found that it had no value in stimulating epithelial regeneration.

Effect of Enzymes

The role of enzymes in wound healing is obscure. Fell & Danielli (1943) have shown by histochemical and chemical tests that a high concentration of phosphatase is present in the invading polymorphs round a wound, in the scab, and in the regenerating connective tissue, especially at about the fifth day. The role of phosphatase might be expected to be of greatest importance in the healing of fractures, and Blum (1944) has shown that experimental fractures treated with phosphatase, and with a suitable substrate such as calcium glycerophosphate, healed more quickly than controls.

A reduced amount of phosphatase has been demonstrated in the costochondral junctions of scorbutic animals by Bourne (1943) who suggests that ascorbic acid may play some part in the formation and stabilization of alkaline phosphatase, and may allow the production of a phosphatase-impregnated bone-matrix, upon which bone-salt is deposited in the process of healing of fractures.

Wounds treated with the enzyme mucinase, by Berenblum & Duthie (1940), showed increased transudation of fluid and an increase in area, but the progress of healing was unaltered.

Effect of Proliferation-promoting Factors

The suggestion that injured cells liberate substances which stimulate cellular proliferation in the neighbourhood of the injury was first made by Wiesner in 1892 and has received strong support from experiments with plant-tissues. One such substance, to which the name "traumatic acid" has been applied, has been isolated from the bean-pod (English & Bonner, 1937), and has been shown to have the chemical structure Δ^1 -decene-1,10 dicarboxylic acid (English, Bonner & Haagen-Smit, 1939).

The occurrence of such materials in animal tissues is much more obscure, but suggestions have repeatedly been made that injured tissue-cells liberate factors variously termed "wound hormones," "necrohormones," "archusia," "trephones," "desmones," "cytopoietines," etc., which initiate repair at the site of injury. This subject has been reviewed by Davidson (1943). It must be emphasized that the existence of such materials has never been definitely proved, and that none of them has been chemically characterized. At the same time, some of the evidence adduced for their existence is not without interest. Fischer (1930), for example, has

² [For a critical review of claims made for ascorbic acid, see a previous paper by Dr S. S. Zilva (*BMB* 487)—Ed.]

shown that tissue-cultures which were repeatedly wounded mechanically grew more quickly than controls, and that saline extracts of such wounded cultures could revive growth in cultures in which growth was latent. This observation has been confirmed by Suntzowa (1944) Fischer (1941) has concluded that "the liberation of substances with growth promoting properties which are set free by the mutilated cells" is one of the factors involved in the process of regeneration

A similar view has been put forward by Carrel (1922, 1924, 1930), who has shown that cultures of leucocytes produce protein derivatives which stimulate the proliferation of epithelial cells and fibroblasts. He suggested that such materials or "trephones," which may be similar to the growth-promoting principles of embryo-tissue juice, are liberated by the leucocytes in the neighbourhood of wounds and act as stimulants to growth and proliferation. It should, however, be emphasized that the products of protein-breakdown can stimulate the growth of fibroblasts *in vitro* (Carrel & Baker, 1926, Willmer & Kendal, 1932, Davidson & Waymouth, 1944), and it is not unreasonable to suppose that such products abound in the vicinity of dying or injured cells, without necessarily being elaborated by the cells as a specific response to injury.

There is some evidence that the plasma of the wounded organism contains factors which stimulate the growth of tissue-cultures (Akamatsu, 1922) and the process of wound-healing (Lonn-Epstein, 1927). Such substances have been held to be responsible for the more rapid healing of repeated wounds and fractures in man than of primary wounds. If such factors exist, they might be expected to be abundant at that stage in wound-healing when proliferative activity is most vigorous. To test this hypothesis, Young, Fisher & Young (1941) measured the rate of closure of experimental wounds in rabbits, secondary wounds being made 10-12 days after the primary wounds. These secondary wounds healed more rapidly than the primary ones in a statistically significant number of cases. This observation has been confirmed by

Sandblom (1944) who measured the tensile strength of the healing wounds. While these observations are both interesting and suggestive, it must be kept in mind that there is as yet no clear-cut evidence that the formative stimulus to growth and proliferation is definitely chemical in nature, and the question of the existence of "wound hormones" must in the meantime remain merely an hypothesis.

Effect of Embryo-extract on Wound healing

Since the early observations of Carrel (1913) that the juice of embryonic tissues will stimulate markedly the growth of tissues *in vitro*, attempts have been made to employ embryo juice to accelerate the healing of wounds. Favourable results have been reported by Bergami (1925), Carrel & Baker (1926), Carnot & Ternis (1926), Roulet (1926), Wallich (1926), Schloss (1928), Kiaer (1927), Nakamura (1930), Bugliari (1927), Amorosi (1931), Morosov & Striganova (1934) and Egorov (1943), but not by Dvorak & Byram (1930) nor by Auerbach & Doljanski (1944).

Fischer (1939, 1940) has claimed to have purified the active principle from beef embryos, and has named it "embryonin" (Fischer & Astrup, 1943). An adsorbate of this active principle on kaolin has been used to accelerate wound-healing by Waugh (1940) and by Nielsen (1939), but the results of both these workers have been criticized by Young, Fisher & Young (1941). Botsford (1941) found that such a kaolin adsorbate caused no increase in the tensile strength of healing wounds in dogs, while Dann, Glücksmann & Tansley (1941), in a carefully controlled series of experiments on rats, showed that the adsorbate did not greatly affect the decrease in wound-area, nor the rate of epithelialization, although it caused marked improvement of collagen- and muscle-regeneration. Willmer has shown that the kaolin adsorbate stimulated the migration, but not the division, of cells *in vitro* (Willmer, 1942, Dann *et al.*, 1941).

It is in any case doubtful whether any attempt should be made to accelerate the rate of healing of a wound which is healing under normal conditions.

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REMARKS ON THE GROWTH AND HEALING OF BONE

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Literally hundreds of papers on this subject have appeared in modern times but in spite of this remarkable flow we are very far from reaching a solution of all the problems. The old experimental work was chiefly observational, but much of it is worth recalling because it is good and because the same experimental methods have been used in recent investigations. A century ago histological methods were introduced which led to descriptions of the mode of bone growth and repair, and also started the controversy about osteoblasts and osteoclasts. The development of x-ray technique and chemical methods next focused attention on the mineral constituents. The discovery of the enzyme, phosphatase, tended further to concentrate work on the inorganic materials. Bone, however, is only about one half mineral matter, the other half, collagenous material, is not susceptible of analysis by ordinary methods, although x-ray crystallography is beginning to give information about its structure.

In the following account it is proposed to deal almost entirely with experimental findings on bone growth and bone healing. Because of the difficulty in obtaining controls in human cases much of the work to be described has, of necessity, been carried out on animals. Some of the experiments have, however, been repeated in human beings when the results justified this course. It will be granted on general grounds that the conditions for good growth of bone are likely to be those needed for satisfactory bone healing. Accordingly, no attempt has been made to separate the problems of growth from those of repair, especially as growth is so much easier to measure than is repair.

Early Experiments on Bone Growth and Repair

The history of the development of modern ideas on the growth of bone has been described in a truly fascinating manner by Keith (1919). Belchier (1735-36), a London surgeon, was the first to note that madder (*Rubia tinctorum*) stained the bones of living animals. Duhamel (in papers to the French Academy, 1739-43) exploited this discovery and concluded that only the bone formed during madder-feeding was stained, and deduced that bone was laid down in layers around the shaft. By fracturing bones and feeding madder to the animals he found that the callus and new-formed bone was derived chiefly from the periosteum. It was not until John Hunter (from about 1750 to 1770) repeated the madder experiments and carried out others on growth in length by implanting metal pellets in the shaft of the bones, that the modern conception of bone growth was reached. This is that growth in length occurs only at the extremities, while increase in girth is due to the deposition of bone externally accompanied by the absorption of bone from the internal surface. The alterations in the shape of the bones which occur throughout life are produced by modelling, a controlled process of deposition and removal of bone. The part played by the bone cells was described by Goodsir in 1845, by which time the microscope was coming into general use in biology.

Further advance was postponed until the development of antiseptic and aseptic techniques, as sepsis must have ruined many of the early experiments. Macewen (1912) was thus enabled to carry out on human beings and on dogs experiments which resemble recent work in a surprising way. He removed the shaft of a humerus affected by osteomyelitis from a boy aged 3 years. About two years later (in 1880), because no bony growth had occurred, he implanted along the site of the humerus a row of pieces of bone obtained from six boys who had had tibial wedges removed for the correction

of rachitic deformities. The bulk of the fragments had no periosteum, yet they "took" and the boy developed in due course a very useful limb only slightly shorter than its fellow. Again Macewen took a piece out of the radius of one dog and, after removing the periosteum, he broke the piece up into fragments and implanted them into an experimental gap in the radius of another dog. The grafts took and the radial shaft was restored. These experiments were designed to show that the periosteum did not form bone, but this aspect of the problem is now only of historical interest. Macewen insisted that the so-called epiphyseal discs should be called diaphyseal discs, and he demonstrated by experiments on dogs that they contributed to the length of the shaft and not to the epiphyseal growth.

Self-differentiation of Bone in Growth and Repair

Coming now to more recent work it is best to begin with the investigations of Miss Honor Fell and others on the development of bones in tissue culture. It was found (Fell & Robison, 1929, 1930, Fell, 1932, 1935), that the isolated femora of 5½- and 6-day chick embryos had a remarkable power of self-differentiation. In tissue culture these bones, in spite of the loss of blood supply, and the absence of muscular pull and of all relationships with other tissues, grew to three times their original length while still retaining their normal gross anatomy. The general form of the bone must, therefore, be determined by intrinsic factors. These tissue-culture experiments have settled the problems of the osteogenic function of the periosteum and the status of the osteoblast, because it was found that both the periosteum and endosteum of the chick (before and after hatching) can form bone *in vitro*, whereas a culture of fibroblasts never forms bone.

This power of self-differentiation—described by Hunter as a form of "consciousness"—diminishes with age, but the human child at birth has a remarkable power of repair. A birth-fracture of the femur may be firmly united in 2 or 3 weeks, and even if it be allowed to unite with the fragments literally at right angles to one another, and with gross overlapping, yet in 6 to 9 months the radiologist will find it difficult to say which femur has been fractured (White, 1944). It would not be wise, however, to regard all the power of determination of shape as being resident in the bone itself, because in an infant a massive involucrum, formed as a result of acute osteitis with necrosis of the entire diaphysis, may in a few months be so altered in size and shape that it resembles closely a normal bone. In another case of acute osteitis the shaft of, say, the radius may be lost and will have to be replaced by a graft from the tibia, yet quite soon the graft may take on the typical appearance of the radius with a normal medullary cavity (White, 1944). If this is a matter of chemical organizers, such as those which are involved in the formation of the lens of the eye in the embryo, then we may have the clue here to the solution of many of our problems. This, however, may be asking the scientist to discover the elixir of youth.

There are substantial grounds for thinking that the problem is humoral rather than nervous. Nervous influences on bone growth are well known, but their effects are not very great. In cases of anterior poliomyelitis the bones of the paralysed or partly-paralysed limb are smaller in all dimensions than those of the sound limb. This difference can easily be seen in growing cats whose ventral spinal roots have been cut (Bell, Chambers & Robertson, unpublished data). Lesions of the postcentral gyrus in children are regularly associated

with "a comparative moderate smallness of the contralateral part of the body" even when the precentral gyrus is normal, such cortical lesions do not, however, produce such marked alterations in size as do spinal lesions (Penfield & Robertson, 1943). The general experience of orthopaedic surgeons is that operative fractures of bones affected by poliomyelitis heal just as rapidly and well as fractures of normal bones (Barnes, personal communication), in spite of the nervous and vasomotor disturbance.

Healing of Fractures in Tissue Culture

Following up Miss Fell's work on bone growth, Miss Niven studied the repair of fractures in tissue culture (Niven, 1931), using chick and mouse embryonic material. In 5-day-fowl "bone" rudiments with cartilaginous shafts, repair occurred by chondroblasts and no trace of the injury was left. In 5½-day rudiments, repair did not take place by chondroblastic activity but by osteogenic tissue laying down osteoid tissue peripherally, and sometimes in the gap between the cut ends. In spite of the disturbances due to the fracture and its healing, normal growth (for conditions *in vitro*) and normal histogenesis of cartilage and bone occurred. In the nearly full-time mouse, cortical bone was repaired by osteoblasts, the deposit of bone being thicker than in the case of the fowl rudiments. It was noticed that if a healing fracture became angulated, more bone was laid down in the concavity than on the convexity of the bone, this was considered by the author to be due to the pull of the perichondrium or of fibrous-tissue bands between the ends. This laying down of bone in the concavity occurs also in bowed rachitic bones, and it seems to the present writer very like what one would expect from Wolff's (1892) law which has been paraphrased by Keith (1919) thus: "The osteoblasts at all times build and unbuild according to the stresses to which they are subjected." It is, however, hard to imagine any force acting *in vitro* comparable to the stresses involved in weight-bearing or muscular action. The early failure of the reparative powers of cartilage may be partly responsible for the lack of success with cartilage-grafts (Mowlem, 1941).

Histological Features of Bone Healing and the Influences of Bone Grafts

The orthodox description of the process of repair of a fracture is clearly given and well illustrated by Watson-Jones (1943). First the haematoma between the bone-ends is invaded and absorbed by granulation tissue. This is replaced by hypertrophic cartilage formed by the periosteum and the endosteum. Bone cells and bone matrix then gradually appear, and an almost tumour-like mass of irregular cartilage and bone is laid down. This stage of primary callus gives union in about 2 or 3 months in adult life. The primary callus is in turn replaced by "mature" or lamellar bone, which is laid down in the lines of stress, i.e. in the lines of the original lamellae, the bone in the medullary area is reabsorbed and the tubular shape is restored. Union by this lamellar type of bone takes from 4 to 5 months.

A few details have been added by Urst & McLean (1941a, 1941b) and Urst & Johnson (1943) who have examined material from both animal and human fractures by histological methods which do not require decalcification. In the early stages of repair in animals osteoid matrix is calcified as quickly as it is laid down, provided that the diet is adequate in minerals. In man, osteoid tissue is laid down faster than it can be calcified, suggesting that at this stage it is formed at a greater rate than that at which the calcification mechanism can operate. At a later stage the calcification mechanism keeps pace with osteoid tissue formation.

Bone grafts probably owe their success to the small amount of reaction produced in the tissues by their presence. A living autogenous graft is undoubtedly better than a boiled dead one, although the use of such a graft has often been completely successful. Even a living graft seems to die quickly—if death can be deduced from the disappearance of cells from the bone lacunae. The graft does not take up dyes which have an affinity for bone neither does it show "decalcification" when the neighbouring bones show it. These are not unequivocal evidences of the death of the graft but it is generally agreed that the cells of the endosteum and periosteum may continue to live and contribute something to the repair. Baker (1939) describes, with photographs of

bone sections, the revascularization of a graft and its incorporation into the newly formed bone.

Work by Mowlem (1944) makes one wonder if the transplant always dies. He took a block of bone from the ilium and, after discarding the cortical bone, broke up the cancellous bone into chips. These were used to repair mandibular and tibial defects. In the case of the mandible, x-ray photographs showed that fusion began to be visible between the chips and the bone-ends in about 14 days, the average time for the removal of all splintage was 26 days. Mowlem claims that this very quick repair suggests very strongly that the cancellous chips actually live and acquire a blood-supply early.

It may be that Macewen in his grafting experiments, already referred to, owed his success to the fact that he used cancellous tissue from the interior of the bone. It is interesting to find that both Mowlem (1944) and Converse, Clarke & Guidi (1944) recommend—as did Macewen about 50 years ago—that bone chips should be used to fill cranial defects.

Further evidence that bone chips are not just inert sources of calcium salts are these. Macewen found that bone dust was not so effective as were bone fragments. Bisgard & Macumber (1940) cut out blocks from the radial bones of rabbits and replaced them with pieces of costal cartilage. In addition, on the right side, bone ash derived from rabbit bone was inserted to help to fill the defect. This procedure did not aid the repair process.

These findings and others could be explained by supposing that the calcium phosphate of dead bone is not used directly but is first absorbed into the blood-stream and then laid down in living, i.e. vascular, bone. If this be true then either it must be a balanced process or it must occur very slowly, as there is very little disturbance of the calcium metabolism at the time of healing (Cuthbertson, 1930).

Phosphatase in Bone Growth and Repair

The product of the calcium and phosphate ions in blood is normally equal to the solubility product, so that any local increase of phosphate ions will cause a precipitate of calcium phosphate. This increase of phosphate ions in ossifying tissue seems to be provided by the action of the enzyme phosphatase on un-ionized phosphoric acid esters. Robison has found (Fell & Robison, 1929) that even in tissue culture the isolated chick-femur can produce phosphatase, probably in hypertrophic cartilage cells, but cartilage which is not destined to ossify does not produce phosphatase (Fell & Robison, 1930). The enzyme phosphatase cannot be the whole key to the secret of ossification because, although both the kidney and the intestine contain phosphatase, yet conditions are not suitable for bone formation.

Stirling (1931) found that the phosphatase-content of the fracture-haematoma was the same as that of the blood. There was no difference between the blood phosphatase of normal and fracture cases. The pH of the haematoma tended to become acid because of accumulation of lactic acid, but after 10 days or so it returned to the normal or even to the alkaline side of neutrality, at which enzyme-action would be expected to be greater.

Botterell & King (1935) investigated the phosphatase-content of healing fractures in rabbits. They found that there was an increased phosphatase-content which persisted for 50 or 60 days. The increased phosphatase-content of a repairing fracture seemed to accompany the formation of hypertrophic cartilage cells, osteoblastic activity, and the formation of bone matrix. The introduction of phosphatase into experimental fractures produced no change in the rate or quality of calcification. Blum (1944) filled gaps made in the radius of rabbits with phosphatase and glycerophosphate with an alginate gel to prevent the too-rapid diffusion of the enzyme. The treated fractures showed acceleration of bone repair as compared with the controls.

Delay in the ossification of a healing fracture might conceivably be due to a lack of substrate rather than to a lack of phosphatase. Stirling (1931) injected a mixture of calcium and magnesium phosphates into the fracture-haematoma in animals and in man but was not convinced that he had increased the rate of healing. Armstrong, Sperling & Litow (1942) injected rabbits with sodium beta glycerophosphate; the fractures showed a larger callus in the treated (as compared with the controls) with a better bridging of the defect. This method is not likely to be successful in man because it

has been shown by many workers that the blood-calcium in man is within normal limits in cases of fracture, and that the blood-phosphorus may be slightly raised (Cuthbertson, 1930, Stirling, 1931)

The phosphatase-content of the haematoma is decreased and healing is delayed in the presence of infection (Tollman, Drummond, McIntyre & Bisgard, 1940, Drummond, Tollman, Bisgard & Ross, 1940) Materials which depress phosphatase activity should not be used as internal splints—stainless steel and certain plastics do not have this defect (Blum, 1944)

The injection of procaine into a fracture-haematoma to reduce the pain of reduction interferes with the course of events in the haematoma (Stirling, 1931) On the other hand, Bohm & Flyger (1943) injected procaine into fibular fractures at regular intervals extending over 3 weeks, and found that this procedure promoted the consolidation of the callus It may be that the effect of procaine is general rather than local, because Popov & Ivanov (1941) reported that injections of this drug, made either near the site of fracture or distally, increased the rate of callus formation

Radiological Appearances in Fractures

Radiologists are well aware that the density of the shadow of a bone depends on its content of calcium salts, but they are tempted to interpret shadows with such terms as decalcification, rarefaction, sclerosis, or osteoporosis The description "rarefaction" or "decalcification" is often applied to the lighter shadows of bone near a fracture, and "sclerosis" to the denser appearance of sequestra The fallacies involved in the use of such terms are discussed by Baker (1939) Decalcification in the sense of removal of salts without removal of matrix does not occur, hypocalcification of the matrix occurs in rickets but it is not due to decalcification but to inadequate calcification of the matrix When bone is eroded by osteoclasts, all the bone tissue (i.e. matrix plus calcium salts) is removed, this is best described as de-ossification It is not possible for the radiologist to distinguish between a simple thinning of the bone and osteoporosis—in which the bone channels are widened by osteoclasts

The femora of rats fed on diets of high and low calcium-content (adequate in other respects) showed great differences in x-ray shadows (Bell, Cuthbertson & Orr, 1941) It was proved by measurements of size and strength and by chemical analyses that the bone material was the same in all cases, and that the x-ray differences were due simply to differences in thickness of the femoral walls The striking constancy of the physical and chemical characters of bone was further demonstrated by experiments in which alterations of bone growth in rats were produced by injecting pituitary extracts, oestradiol, parathyroid hormone or by feeding thyroid extract (Bell & Cuthbertson, 1943) Rickets is the only condition in which alterations of bone-quality have been demonstrated in this laboratory (Bell, Chambers & Dawson, unpublished data) Sequestra are often described as "sclerosed," but analyses of cleaned fragments show that there is no significant difference between them and healthy cortical bone (Baker, personal communication) Another difficulty for the radiologist is that union may occur by callus containing little or no calcium, which casts a very poor shadow (Ham, Tisdall & Drake, 1938), but this is not likely except when there is shortage of vitamin D

Nutritional Effects on Fracture-healing

There is no doubt that defective nutrition interferes with the healing of a fracture, but under modern conditions protein, mineral or vitamin deficiencies are easily overcome and are not likely to be limiting factors The problem is to find whether any dietary modification can accelerate healing

Even fairly severe deficiencies of protein (Armstrong, 1944) and of minerals (Goisman & Compere, 1938) do not retard healing Lysine deficiency appears to diminish the growth of epiphyseal cartilage (Harris, Neuberger & Sanger, 1943)

Deficiency of certain of the vitamins undoubtedly hinders bone repair Hertz (1936) gives a historical account of these deficiencies and describes his own investigations A summary has recently been given by Harris (1944) Vitamin-C deficiency inhibits repair very markedly by reducing the formation of bone matrix Bourne (1942, 1943) measured

the regeneration of bone and found that neither vitamin C nor calcium salts accelerated healing in rats on an adequate diet, but that calcium ascorbate injected subcutaneously in rats did increase the amount of bone regenerated up to the seventh day Vitamin C may play a part in the formation or stabilization of phosphates as well as in the formation of matrix In rickets there is delay in healing The general opinion is, however, against the use of large doses of vitamin D in the treatment of fractures (Stirling, 1931, Hertz, 1936)

Deficiency of vitamin A produces very striking changes in growing pups with a disturbance of the process of bone modelling (Mellanby, 1944) Although the vertebrae and cranial bones increase in external dimensions as in normal growth, absorption from their inner aspects is diminished and hence does not allow for the growth of the nervous system Bony overgrowth occurs in many places, nerves become compressed and they degenerate with, as a consequence, loss of vision, loss of hearing and inco-ordination of movements There is no evidence that large doses of vitamin A have a favourable influence on bone growth or healing

Other Factors which might Influence Bone Healing

Although oestrogens have been found to increase the thickness of the walls of the bones (Gardner & Pfeiffer, 1938) it is not always possible even with large doses of oestrogens to increase bony deposition (Bell & Cuthbertson, 1943) Pollock (1940) has reported that the administration of theelin accelerates the firm union of fractures in rats Silberberg & Silberberg (1935) found that the injection of extracts of the anterior pituitary gland into young guinea-pigs accelerated bony repair in 80 % of cases It is easy to imagine, however, that prolonged oestrogen or pituitary therapy in human beings might have unpleasant consequences

Leriche & Policard (1928), Grieg (1931) and Watson-Jones & Roberts (1934) have attempted to explain bony changes in terms of vascularity and have proposed various "laws" With increased blood supply, they say, there is decalcification, with decreased blood supply, increased calcification, and in the absence of a blood supply calcification is unaltered This is too simple a theory to fit all the facts, and the reasons for not accepting it are well summarized by Baker (1939) Pearse & Morton (1930) showed that ligation of the deep veins from the part hastened the healing of the fractured fibula in the dog, but that hyperaemia produced by lumbar sympathectomy did not have a constant effect on the rate of bone healing (Pearse & Morton, 1931) The clinical results of intermittent venous stasis were not convincing, although sometimes there was a stimulation of callus formation

Conclusions

It is not possible to give any useful summary of our knowledge of bone healing Even if we go to extremes and consider the supposed causes of non-union, we find that there is little information of a positive nature Anderson & Burgess (1943) say that delayed union is 90 % preventable Both they and the Subcommittee on Healing of War Fractures (Medical Research Council, 1944) are of the opinion that too active treatment is to be avoided, once the fragments are put into position they should be left alone

Surgeons have varied greatly in their advice about immobilization of fractures There seems to have been no experimental investigation of complete versus partial fixation of broken bones Dogmatic statements that inadequate immobilization is the main cause of delayed union should be regarded with reserve

More attention should be given to the bone matrix and to measurements of the strength of healing fractures The preoccupation of the chemists with the easily determined minerals has led to a tendency to regard bones as a store of readily-available calcium and phosphorus, rather than as one of the important supporting tissues of the body But, for the patient with a broken bone, or the surgeon in charge of him, the strength of a healing fracture is an exceedingly practical matter

The problem, though at present baffling, is not likely to be left as it stands, because any method which could regularly induce even a small increase in the rate of bone healing would be of great economic value

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THE EXPERIMENTAL STUDY OF SKIN GRAFTS

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The plastic surgeon has in the past relied upon the laboratory worker neither for inspiration, principle, nor technical aid. It is a matter of historical fact that the principles upon which his work is founded were discovered and first formulated by himself. The most instructive of these principles is that the so-called "natural" or unaided processes of healing, in injuries exceeding a certain degree of severity, are either non-existent or totally inadequate. Everybody realizes that one cannot regenerate a nose, but the plastic surgeon was the first to teach that one cannot regenerate the full thickness of true skin. The plastic surgeon's solution for the second of these disabilities is just as important as his more spectacular solution for the first, although the remaking of noses and jaws will always represent, in the popular mind, the summit of his art.

In the short account which follows, no distinction is made between "clinical" and "laboratory" experiments on skin-grafting. The former are not so imprecise, nor the latter so remote from clinical practice, as to make the distinction a useful one.

Some Problems of "Incomplete" Grafting

Severe burns, which have as a consequence the widespread loss of skin, are among the commonest injuries of warfare. Their definitive treatment is an operation for the replacement of lost skin. When, because of its great extent, a raw area cannot be fully covered by the patient's own skin, the plastic surgeon has in theory the choice between several possibilities. The one to be considered in this section is the makeshift operation of "discontinuous" or 'incomplete' grafting (no commonly-used term describes all its varieties). In this procedure, the raw area is seeded with little bits of skin which eventually coalesce by reason of their outgrowth, to form a complete covering of epidermal epithelium.

Pinch grafts—round buttons of skin about 4 mm. or 5 mm.

in diameter, which taper from full dermal thickness in the centre to epidermal thickness at the margin—are the most widely used, for this purpose, of a great variety of different types of skin fragment. The advantages of pinch grafts are well known. They are very economical of skin, they are easy to cut and plant, they sometimes live on raw areas where continuous sheet grafts do not, possibly because of the excellent drainage they afford, and, should a single pinch graft fail to survive, its failure does not prejudice the success of another. Pinch grafts nevertheless share with other incomplete grafts certain unavoidable defects. There is a latent period before outgrowth begins, during which the grafts provide cover only for that small proportion of the raw area with which they are in immediate contact. The new "skin" which does eventually develop between the grafts is both functionally and cosmetically of inferior quality. A defect peculiar to pinch grafts is the permanent scarring or pock-marking of their donor area. This at least can be avoided. Gabarro (1943, 1944) points out that rectangular pieces of a small thin continuous sheet graft, such as is normally used for skin repair where cosmetic considerations take second place, can often be substituted with advantage for pinch grafts. In practice, he recommends that the rectangles should be of the size of postage stamps. Being thin, the grafts take well, and their spacing apart makes for good drainage.

There is another and quite different solution with its own special disadvantages and drawbacks to the problem of making one piece of skin do the work of two or three. This is to thrust the burden of proliferation upon the donor area rather than upon the grafts. A single donor field may indeed be made to give as many as six successive crops of skin with as little as three weeks interval between one harvest and the next (Brown & McDowell 1941, 1942). Thus a raw area may in time be completely covered by continuous sheet grafts cut repeatedly from the same donor area.

The two solutions we have just considered were founded upon the use of *autografts*—of the patient's own skin. A third possibility is to use the skin of another person. It will not, as a rule, be limited in quantity, and the normal operation of grafting will be in all respects unmodified, save that the skin that is used, a *homograft*, will be taken from someone other than its intended recipient.

The earlier plastic surgeons made no critical distinction between the use of autografts and of homografts, but one may trace in the history of skin grafting (see the review by Medawar, 1943) how an uncritical belief in the success of homografts has given way, through various degrees of doubt, to an almost universal belief in their inevitable failure. In recent years, the use of homografts has indeed found only two champions. Binhold (1939) transplanted single pinch grafts between no less than 157 distinct pairs of human volunteers, in such a way that each graft fitted neatly into a raw area just large enough to receive it. He claimed that 51 were successful, irrespective of blood-group relationships. It is almost certain, however, that the epidermis of his homografts was insidiously undermined and replaced by native epithelium from the margin of the raw area. Sachs & Goldberg (1943) report 65–75 % successful results with infant foreskin grafts transplanted to adults. Their grafts have, in photographs, just the prominent and dead-white appearance of foreign collagen that has been overgrown by native epithelium. There are, in short, no *documented* records of the success of any skin homografts, save only those transplanted between identical twins (Bauer, 1927, Padgett, 1932, Brown, 1937, Schattner, 1944).

Why do skin homografts fail? According to Loeb (1930), they have an "individuality differential" which reacts with host tissue to form a "homotoxin," which then destroys the graft. The reaction is local, and immune factors play no part in it. It now appears that that part of Loeb's interpretation which is not merely verbal is inadequate or mistaken. Thomas Gibson (unpublished observations) found that, when a human being was twice homografted from the same donor-source, the grafts of second planting broke down more rapidly than their predecessors. Evidently an immune factor does play some part, and this conjecture has now been repeatedly confirmed by a variety of independent trials (Gibson & Medawar, 1943, Medawar, 1944, 1945). A systematic examination of the problem as a whole has led to the following conclusions. Homografts always "take" perfectly—they undergo normal primary healing—in a latent period during which they are not to be distinguished from autografts. In due course, however, they are destroyed: even the collagen fibres of the homograft dermis are eventually dissolved away. In not one of more than 800 trials with 800 distinct pairs of rabbits has a homograft been found to succeed. It can be proved, moreover, that the reaction provoked by skin homografts in rabbits is governed by *at least* seven antigens freely combined among *at least* 127 skin-transplantation groups. The time of survival of homograft skin epithelium varies with the amount of skin that is grafted: other things being equal, skin in high graft "dosages" survives for a shorter time than skin in low dosage. The purely local dosage of the grafted skin is, however, without significance, for one may graft a great quantity of skin to one part of the body and a tiny bit to some place remote from it, and yet find that all the grafts break down simultaneously and in identical fashion. This shows that the homograft reaction is systemic, and not confined to the immediate neighbourhood of the grafts.

The most remarkable property of the immune reaction is that, although grafts of second planting do break down very much more rapidly than those carried by a non-immunized animal, they still do not break down at once. There is evidence that the antibody acts upon some constituent of the nucleus—possibly upon the genes themselves—to which it has no access until the cells of the graft begin to divide. They normally begin to divide between the 4th and 6th days from planting, and grafts on immunized animals live just this length of time.

Another unsuspected property of the homograft reaction may be mentioned here: it appears to be fully developed in rabbits which are only 2½–3 weeks old on the day of planting. The practical significance of this fact will be discussed below.

The evidence of the previous section suggests that homografts are destroyed by some variant of the reaction of "active acquired immunity". There is therefore no immediate prospect of using skin homografts for definitive grafting. It is possible that they still may have some useful function to perform as temporary wound-dressings, e.g. on badly burned children. Kilner (1937) and Brown & McDowell (1941, 1942) have used skin homografts for this purpose.

The experimental work just reviewed makes it possible to suggest a number of principles for the use of homografts as wound dressings. It is clear that the use of pinch homografts is pointless. They provide negligible skin cover until the grafts coalesce by outgrowth. The homograft reaction may overtake them before they do so, and if that happens, the object of grafting in the first instance has been lost. If they do coalesce, then the raw area between the original pinch grafts will be surfaced by epithelium which is abnormally thick and rapidly growing. In other words, when homografts of this type do eventually provide complete cover, the *dosage* of skin they represent is higher than it would have been, had thin continuous sheets of skin been grafted in the first instance. The survival time of the homografts will therefore have been reduced, and valuable time lost. A continuous and complete graft is the only type worth using.

The entire homograft operation must be planned for execution in a single session. The existence of an acquired immunity makes grafting at spaced intervals of time quite useless.

If the baby rabbit is any guide (see above), the human baby is just as resistant to skin homografts as the adult, and as it is small, the foreign skin it bears will be in a relatively high dosage. It is most unfortunate that these circumstances do not favour the use of skin homografts in just the situation where in theory they would be most valuable.

When a homograft has done its duty as a wound dressing, the condition of the patient may be favourable enough for definitive grafting. *All* the homograft tissue, including the dermal collagen, should then be removed. The recipient will remove it if the surgeon does not do so—but to the accompaniment of a prolonged low-grade inflammatory process which may well prejudice the general success and cosmetic quality of the new grafts.

One further possibility may be mentioned. It may not be worth while to use homograft dressings on patients who have received transfusions of whole blood with living leucocytes beforehand. Unless the homograft reaction is rigidly tissue-specific (which is unlikely), and rigidly specific towards the tissues of the particular donor (which is known not to be the case), then the "transplanted" leucocytes may generate an immunity towards transplanted skin. This possibility is now being investigated. Furthermore, until there is evidence that homografting is in all such cases harmless, no homograft dressing should be applied to a woman of child-bearing age. In view of the known behaviour of the rhesus antigen¹ this remark should need no amplification.

Sticking Skin Grafts into Place

The plastic surgeon lays down the firm principle that skin grafts should wherever possible be transplanted to vascular and bacteriologically clean beds and held there under moderate pressure until primary healing is complete. The third of these requirements is not always easy to realize in practice, the tip of the nose and the angle of the jaw are awkward places upon which to put uniform pressure. What is needed is a strong innocuous physiological "glue," such as that provided by blood plasma (if its fibrinogen content is increased) or, as recent work makes possible, by strong solutions of fibrinogen itself. The glue is in any event applied as a fluid to the underside of the graft immediately before the graft is laid into its bed. It percolates into the apposed surfaces and clots to form a moderately tenacious fibrin jelly. The clotting process may be hastened and made more uniform by mixing the fluid plasma, immediately before use, with calcium chloride solution, viper venom, tissue extract, or thrombin, the choice of coagulant will depend upon the treatment which the plasma received on withdrawal in order to keep it fluid.

¹ [For a review of present knowledge of this antigen, see BMB 420—Ed.]

The first published reports of the use of fibrin glue for skin grafting are those of Sano (1943a, 1943b). Sano recommends the use of the patient's own plasma, kept fluid by immediate mixture with a solution of heparin in Tyrode solution,¹ and caused to clot *in situ* by applying to the graft-bed a macerated preparation of the patient's erythrocytes and leucocytes, also in Tyrode. Sheehan (1944a, 1944b) has reported very favourably upon his clinical trials of Sano's original technique.

As the theoretical advantages of using macerated leucocytes as stimulants of growth and repair do not withstand close investigation, the clotting agent may well be replaced either by more concentrated tissue extracts or, preferably, by solutions of thrombin. The fixation of grafts with blood-bank plasma and thrombin has been described by Tidrick & Warner (1944) and by Young & Fatava (1944). The rapid clotting so achieved is an improvement, but it does not overcome the most serious defect of Sano's original technique, namely, that an unfortified plasma clot is too flabby and tenuous to make a really safe glue. It was this disability that led the writer to introduce fortified plasma, i.e. plasma with its fibrinogen content artificially raised, for repairing severed nerves (Young & Medawar, 1940, Seddon & Medawar, 1942). The simplest solution for the problem (Cronkite, Lozner & Deaver, 1944, Sano, 1944) is to use strong solutions of dried reconstituted human fibrinogen clotted with human thrombin. The technical difficulties of preparing these reagents are being overcome.

Further Possibilities in Skin Grafting

The writer would like to put forward for consideration some ideas on the technique of skin grafting which are still in process of experimental verification. They are relevant to the interpretation of the results obtained from the technique of fibrin fixation.

A free skin graft spends a preparatory period of its life *in situ* in an ischaemic condition, deprived of a free circulation of blood and of any supply of oxygen save that small quantity which may diffuse through the cuticle on the one side or the full thickness of its dermis on the other. It remains in this condition until an effective blood-supply

¹ ["Tyrode" is essentially a Ringer's solution with added phosphate and bicarbonate, it is tedious to make and cannot be sterilized by heat. As the graft bed can assimilate a thick dusting of the relatively insoluble sulphanilamide powder in a matter of hours, one may guess that Tyrode, together with its theoretical advantages, is removed and replaced by oozing and diffusion in a matter of minutes. In other words, normal saline can be substituted for Tyrode without loss.]

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* [BMB 118]

reaches the underlying dermis, i.e. for a length of time which is roughly proportional to the thickness of the graft. The upper working limit to the thickness of free skin grafts is evidently set by the rate of upward surge of the capillaries on the one hand, and the resistance of the superficial epidermis to ischaemia and ischaemic autolysis on the other.

In order to make certain that a thick skin graft should heal without local "trophic" ulceration, and to make possible the use of thicker skin grafts than hitherto, one may attempt either to accelerate the process of vascularization, or to prolong the resistance of the epidermis to generalized autolytic changes. There is no known solution for the first problem, but (apparently) a very simple solution for the second.

The length of time which skin can survive in the absence of food and oxygen is a function of its temperature—at least within the physiological range 0° C–37° C. The higher the temperature, the shorter the time of survival. In the refrigerator, for example, a skin graft remains viable and therefore transplantable for at least three weeks in the absence of oxygen. At the temperature of the body, it would long since have destroyed itself. Now skin grafts are normally held in place by pressure-dressings, very often involving the use of pads of cotton wool, and in any case serving to keep the graft surface at just the temperature at which its survival-time is most curtailed—the temperature of the body. Some form of open net dressing should therefore be devised, through the gaps in which the surface of the graft would be exposed to the relatively cool air of the room or ward, or separated from it at the most by thin foil or thin transparent sheeting of high thermal conductivity. Under these conditions, with the graft surface only a little above the temperature of the room, the survival time of the graft might very well be more than doubled. The rate of vascularization should not be significantly affected, for the graft bed will be at body temperature, and in fact the graft will display, in vertical section, a gradient from body temperature at the level of the graft bed, where it should be warm, to room temperature at the graft surface, where it should be cool. Fibrin fixation, if after extensive clinical trials it proves to be efficient, is the most obvious way of securing these advantages. Indeed, Sheehan (1944b) uses for his fibrin stuck grafts just the sort of dressing that is theoretically required—a wide-mesh rubberized tulle.

The writer is at present attempting to give a quantitative expression to these generalizations. They are published at this early stage in the hope that plastic surgeons may devise dressings which will realize the theoretical requirements for a "cool surface" graft, and so allow the use of thicker free grafts than has hitherto been thought possible.

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* [BMB 117]

THE BIOCHEMICAL LESION IN THERMAL BURNS*

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The study of burns has a long history. It might indeed be thought that there are few experimental discoveries of importance to be made and that a biochemist is rash to

* [Based upon lectures given to the Alembic Club and the Medical Society at Oxford in 1943 and February 1944.]

venture into such an eminently practical field. Yet until some of the modern biochemical advances have been applied it is not certain that everything has been done to help the burned patient. Study of the pathology of the biochemical lesion can hardly fail to extend fundamental knowledge as

well as lead to practical applications in burns, and even in other obscure skin-conditions

Work on this problem has been carried out in the Oxford department of biochemistry under the aegis of the Burns Sub-Committee of the War Wounds Committee (Medical Research Council), it was planned and directed by the writer to throw light upon aspects of burns other than infective

The Biochemical Approach

Like other workers upon fundamental aspects of burns, we have studied the basic problem of the burn toxin. Briefly, was Underhill right in thinking that the haemo-concentration was the main pathological change (Underhill, Kapsinow & Fisk, 1930)¹ or were those who believed in the toxin theory (Robertson & Boyd, 1923)² to receive support, and can biochemistry settle this problem?

The term "biochemical lesion" was first used by Gavrilescu & Peters (1931)³ to indicate the condition induced in brain tissue by lack of vitamin B₁ (aneurin, thiamine). This is one of the more subtle ways in which cell metabolism may meet interference, it is still not sufficiently appreciated in non-biochemical circles how rapidly knowledge of cell enzymes is increasing, biochemical analysis of the tissue may provide evidence of changes in tissue enzyme systems at a point where histological change is still not detectable. In brain tissue taken from the animal convulsing from lack of vitamin B₁, the tissue does not show abnormal histological changes, though a biochemical alteration in the metabolism of pyruvic acid *in vitro* is present and has been proved to be due to lack of cocarboxylase (vitamin B₁ pyrophosphate)⁴. Again, in 1936, a vesicant substance—dichlor-diethyl sulphone—was shown to be selective in its poisoning effect upon the "pyruvate" enzyme component of brain (Peters, 1936b), somewhat resembling iodoacetic acid (also a vesicant) in this respect. In the injury due to burns, which also produces blisters, it is easy to see that knowledge of the biochemical component of the tissue cell most easily damaged by heat is of fundamental interest. It is even conceivable that accurate knowledge might lead to the possibility of partial reversal of the damage.

Histological Observations

After beginning the work on burns early in 1941 with Dr M. C. Manifold, a fruitful line of attack developed from a plan based upon the following considerations. In a burned area of skin, there must be at least two different zones (see Fig. 1), zone I that of complete heat-coagulation, and zone II that of partial heat-damage, injured by temperatures intermediate between that of the burn and that of the tissue (The horizontal line represents the skin surface). Reflection

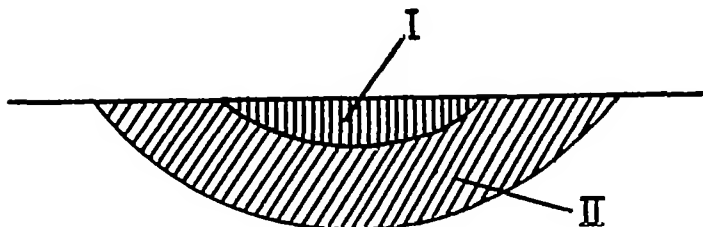


FIG. 1

upon possible burn-toxins shows that zone II is the potentially dangerous area, because undamaged cellular elements (such as enzymes) can be liberated into the circulation, indeed skin proteins may be foreigners in the circulation and therefore unsafe. It is also a zone where reversal might be possible. The apparatus described in Fig. 2 was designed with J. T. Cox to determine the limiting temperatures for this damage. It is similar in principle to that used by McMaster & Hudack (1932) for their studies on lymph flow, though this was not realized at the time. It was soon found (with M. C. Manifold) that there was a critical temperature of about 50° C for applications of the burning-iron to the

shaved skins of rats and guinea-pigs for some 3 minutes. From this we worked out subsequently (for the first time)

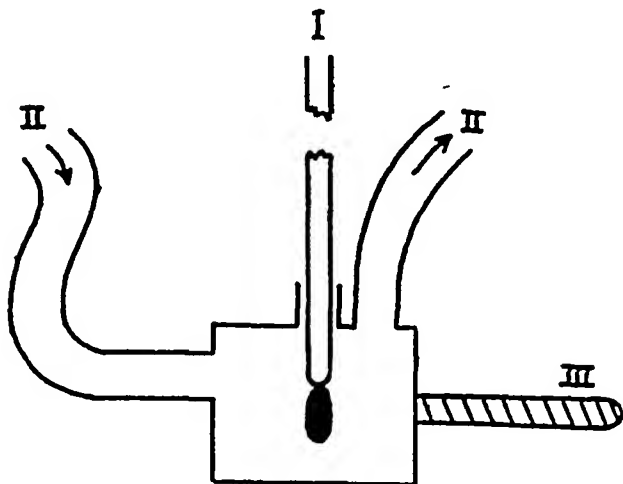


FIG. 2

I = thermometer
II = water
III = insulated handle
[actual size]

the altering pathological responses to increasing temperatures (Leach, Peters & Rossiter, 1943)

TABLE I

[From data of Leach, Peters & Rossiter (1943)]

Shows the rate of development and subsidence of signs after application of heat to skin of guinea-pigs. E. = erythema, Fl = flare, Bl = blanching. Oedema expressed as per cent water content of tissue (average related to normal 100 per cent) found 2 hours after application. Observations at each temperature made on 7 or more animals.

Heat applied for 1 minute Temperature 45°–80° C

Temp. °C	Time after application (minutes)					Oedema, per cent normal, 120	Standard deviation	Histological damage, 120
	0	1	5, 10, 15	30	60			
45	Nil	Nil	Nil	Nil	Nil	103	± 27	A
50	Nil	Nil	E. +	Nil	Nil	97	± 9	A
55	Bl	E. +	E. ++	E. +	E. +	119	± 28	D, E
60 ¹	Bl	Bl	E. ++	E. ++	E. +	180	± 62	F
65 ¹	Bl	Bl	E. ++	E. ++	E. +			G or H
70 and 80	{ Fl. +	{ Fl. ++	{ Fl. +++	{ Fl. ++	{ Fl. ++	(70) 199 (80) 202	± 18 ± 45	H

¹ At 60° C–65° C. for 1 minute there was a separation down to the prickle-cell layer, so that the epidermis could be wiped off.

² Heat coagulation to form a stiff yellow plaque.

³ Three animals observed.

Table I summarizes the main findings for exposures of one minute, and Table II the differing microscopic appearances. There are definite stages of damage, at 50–52° C there is some interference with the cells, oedema appears at about 55° C. At 60° C there is a surface heat-coagulation (which was early observed with Manifold), after lifting off the outer coagulated layer, a punched-out wound with a raw weeping surface is left, this was used by Barnes & Rossiter (1943) (see also Cameron, Milton & Allen, 1943) with success to demonstrate the toxicity of tannic acid in animals. Separation between dermis and epidermis in human burns has been attributed to the formation of steam intradermally—an explanation clearly ruled out here.⁵

In essence there are two types of burns, one involving mainly heat-fixation and the other destruction of cell integrity without fixation, these two types have recently been recognized by Elman & Lischer (1944) and called "wet" and "dry" necrosis. Among the new histological observations emerging from this mode of attack, one may note the demonstration of a reversible swelling of the nucleus, and of migration from the skin after burns, both of substances

¹ [see also Underhill & Kapsinow (1931)]

² [see also Wilson, Macgregor & Stewart (1938)]

³ [For review see Peters (1936a)]

⁴ [Banga, Ochoa & Peters (1939)]

⁵ [W. C. Wilson (personal communication)]

TABLE II—MICROSCOPICAL CHANGES WITH INCREASING TEMPERATURES
[From data of E H Leach]

Stage	Reversible (R) or Irreversible (I)	Nuclei	Cytoplasm	Other effects
A	R	Swelling	Diffuse basophil staining	Infiltration of polymorphs into deeper layers of dermis
B	R±	Collapse (leaving vacuole)	Loss of basophil staining	
C	R?	Further collapse, crescentic appearance		Small spaces between prickle-cells
D	I	Dense uniform staining, pyknosis		Larger spaces between prickle-cells
E	I	Crenated and fragmented karyorrhexis		
F	I	Coagulated		Partial heat coagulation of epithelium, presents rather a normal "fixed" appearance
G & H	I	Coagulated and distorted		Increasing damage to collagen fibres of dermis

staining with "pyronin" and of compounds behaving as nucleoprotein.

It is interesting to note that 70 years ago Cohnheim (1873) made observations on rabbits' ears immersed in a water-bath of varying temperature, with which our observations on skin are in agreement, the comparatively low temperatures needed for damage do not seem even yet to be generally realized. Baumberger, Sultzoff & Cowdry (1942) use temperatures of 50° C. for 2 minutes for separating dermis and epidermis.

It is very important practically to realize the speed at which these changes occur, even one minute after the removal of the heating iron, fluid is starting to enter the tissue. The permeability-changes must be almost instantaneous, Macfarlane (1943) blistered his arm within 30 minutes by exposure to the "iron" for 40 seconds at 55° C. Clearly any first aid aimed at the arrest of tissue-oedema and consequent haemo-concentration should begin very soon, Rossiter (1944) made a careful study of the pressure needed to reverse the entry of fluid in burned areas of small animals, pressures of no more than 10–20 mm Hg, applied for 3 hours immediately after burning, will largely do this, whereas if applied after an interval of 3 hours, pressure is much less effective. The Koch pressure-bandages⁷ and plaster⁸ now advocated should be applied early if swelling is to be prevented. In a recent complete study, Cameron, Allen, Coles & Rutland (1945) report good effects in goats with pressure applied to the limbs, but no effect of graded pressure (10–20 mm Hg) upon abdominal burns.

What Active Products are Liberated by Burns?

Returning to the biochemical lesion, in burns it is possible that there may be actual blocks upon essential metabolic paths in the tissue cells, distorting the normal biochemical state, but in the first instance we have tried to find what biochemical substances might be expected to survive unchanged during the burning in zone II (Fig. 1). Upon the old idea that liberated products might be toxic, enzymes would be more dangerous, as they can induce change in more than their own weight of substrate. For this we had to know more about the true temperature reached in the

* [The writer still thinks that systematic study might produce a composition for first aid, which would dry with the correct elasticity]

⁷ [Siler & Reid (1942)]

⁸ [Barnes & Trueta (1941) Glenn, Peterson & Drinker (1942) Sellers & Willard (1943)]

skin, usually lower than that of the applied "iron". Mendelsohn & Rossiter (1944) have studied this with thermopiles inserted into the skin of guinea-pigs (see Fig. 3)

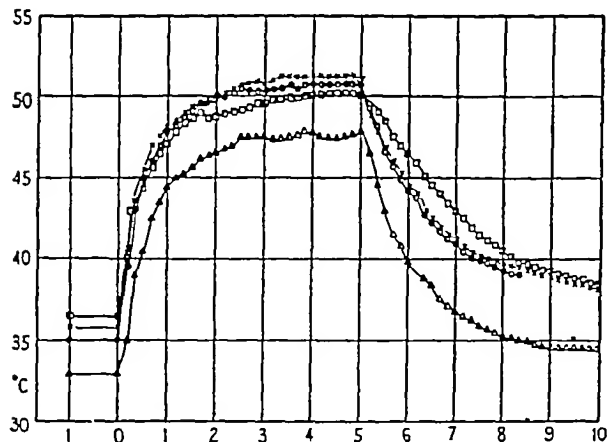


FIG. 3—Time-distribution of subcutaneous temperature under the burning iron (applied during minutes 0 to 5). Temperature of iron 55° C. Guinea pig under nembutal anaesthesia

[From data of Mendelsohn & Rossiter (1944)]

Their report must be studied for their detailed conclusions, it is enough here to state that conditions leading to scab-formation (ie 55° C. for one minute) give intradermal temperatures of 44.5–47.5° C, with an emphasis upon the latter, the temperatures reached are influenced by the initial skin-temperatures, which fall during anaesthesia. Lewis (1927) has already pointed out that in man 47° C. is a critical temperature for pain and that erythema and other changes occur with exposure to still lower temperatures. Hence critical temperatures appear to be not higher than 50° C. for these periods of heating, which sets an upper limit for temperature in an enzyme analysis.

What enzymes survive short exposures to 50° C? Table III embodies our present observations to date upon some isolated enzymes and a few more complete enzyme-systems, it is given to show the trend of results. In these short periods there are marked variations in temperature-sensitivity among these few enzymes studied, conclusions as to temperature stability are more important than those of instability, because it is known that purified enzymes are often very unstable.

Observations upon the temperature-stability of some of these enzymes can be found in the literature for rather longer periods of heating, for instance, Keilin and Hartree (1939) record that cytochrome oxidase is unstable at above 52° C.

For exposures of 30–60 seconds to temperatures causing blistering in man, probably only the pyruvate-oxidase system would be sufficiently inactivated, but three of the enzymes studied were substantially changed by exposure to 50° C for 5 minutes. In preliminary observations upon guinea-pigs, a longer exposure of 6 minutes to the burning iron at the slightly lower temperature of 47° C was not found (with M. C. Manifold) to produce a fall in tissue-respiration in the pieces of skin subsequently removed from the animal. In parallel work in Australia (under Dr Kellaway, with whom we were able to discuss this problem at an early-stage) evidence has been obtained that, with prolonged exposure to heat, the threshold of injury may be as low as 41–43° C (Kellaway & Rawlinson, 1944). These observations throw light upon the problem of the initial change, but do not yet settle its nature. For slightly longer exposures than are needed to produce ordinary burns, 50° C. is just marginal for damage of some of the enzymes studied, it is hard therefore to decide upon the present evidence whether the first change induced by heat is a change in some enzyme or whether it is damage to some lipoprotein complex in the cell interface, though the latter appears to be more probable.

Whichever view is correct, it is evident that there are many enzymes which need not be destroyed by a burn and are therefore capable of liberation in active state from the tissue. Quite often there have been references in the literature to the toxicity of the proteinases, with the contingencies of proteose- and peptone-formation. For this reason, since the beginning of 1943, Miss A. Beloff and the writer have studied proteinases

TABLE III—THE HEAT-INACTIVATION OF SOME ENZYMES BY SHORT EXPOSURES TO TEMPERATURES OF 48–55° C (pH 7.3)
[A selection from previously unpublished observations from the Department of Biochemistry, Oxford]

Enzyme	5 minutes and more			Less than 5 minutes		
	Temp °C	Time of heating	Change %	Temp °C	Time of heating	Change %
1 Enzymes						
Cathepsin ¹	55	5'	– 6.4%			
Skin proteinase ¹	55	5'	– 13			
Amino-acid oxidase ¹	55	5'	– 27			
Succinodehydrogenase ²	54.8	10'	– 57			
Hexokinase (brain) ³	50	5'	Nil			
Cytochrome oxidase ²	49.6	5'	– 48	51.4	2'	– 78%
Malate dehydrogenase ²	49.8	5'	– 71.4	50.7	2'	– 77.3
Lactate dehydrogenase ³	50	5'	– 90.3	50	2'	– 45.5
2 Enzyme systems						
"Pyruvate" (pigeon brain D) ⁴	48	10'	– 22	53	1'	– 6
	53		– 79			
"Glucose" (rat brain B) ⁴	48	10'	– 62			
	53		– 91			
"Succinate" (rat brain B) ⁴	48	10'	– 21			
	53		– 40			
"Glucose" guinea-pig skin ⁴				50	1'	– 16
					(in vivo)*	
				55		– 43
"Glucose" guinea-pig skin ⁵				48.5	3'	– 40
					(in vivo)	

Notes—D = dispersion B = brei (equal volumes cooled liver and ice-cold water) * Burning iron
¹ A. Beloff, 1942–43 ² P. Olafsson, 1941–43 ³ R. W. Wakelin, 1942 ⁴ R. J. Rossiter, 1942 ⁵ M. C. Manifold (preliminary observations), 1942

in skin.⁹ Examination of previous work, including the newer but now classical work of Bergmann and colleagues¹⁰ revealed no enzyme delineated with optimum pH in the physiological range, the proteolytic tissue cathepsins have optima from pH 3.5–5.0 and the leucocyte proteinases act in the acid range (Barnes, 1940). In the belief that a proteinase with the optimum about pH 7.0 must exist, we searched for one. Our adventures are outside the scope of this review. It suffices to say that we have now demonstrated such a proteinase in the skin of man, and of the rat, rabbit, and guinea-pig, so that it is quite general (see note for properties).

Note upon properties of the skin proteinase

This proteinase has a pH activity-range resembling that of trypsin, i.e. is active between pH 7.0 and 8.0, but it is not actually trypsin or chymotrypsin, as it will not digest either benzoyl arginine amide or carbobenzoxy-L-tyrosyl-glycine amide, two specific substrates of Bergmann. It can be distinguished by solubility in KCl solutions from the enzyme hydrolysing leucylglycylglycine, which is also present in the skin extracts, and hence is likely to be different from the enzyme reported by Zamecnik & Graham (1944). It is best prepared by mincing skin with scissors, and drying with ice-cold acetone, from which it is extracted with 5% KCl buffer-solution. Tests for the activity of the proteinase have been made usually by determining the increase in amino-nitrogen, non-precipitable with trichloroacetic acid in casein solutions at pH 7.0, using the Van Slyke technique. According to the recent nomenclature of Bergmann and Fruton, the enzyme will be an amino-endopeptidase, i.e. attacking non-terminal —CONH— linkages.

The skin proteinase fulfils the condition that it could be liberated as a result of burning, because it is comparatively stable to temperatures below 70° C.

Yet, burning the animals causes substantial disappearance of the enzyme from the burned skin (see Table IV), with

TABLE IV—TOTAL CHANGES IN PROTEINASE-CONTENT OF RAT SKIN DUE TO BURNING FOR ONE MINUTE AT 54–66° C, AS COMPARED WITH CONTROL, ETHER-ANAESTHESIA
[From data of Beloff & Peters (1944, 1945)]

Temperature	Time killed after burn (minutes)	Average change %
54–55° C	20	– 3.2
	60	– 23.5
	120	– 32.0
60–61° C	60	– 41.3
	120 & 240	– 54.5
65–67° C	10–20	– 32.1
65–67° C	Before burning (control)	– 4.0

burns at 55° C this reached an average of – 23% and at 60° of – 41% one hour after burning. On the other hand controls heated immediately after killing showed no such effect. Since this disappearance cannot be due to heat-destruction, it must be due either to escape of the enzyme from the cells or to entry of a factor neutralizing the action of the enzyme. Barsoum & Gaddum (1936) found that histamine is liberated in burns.

This is especially interesting in these connections as Rocha e Silva & Andrade (1943) have found that histamine can be liberated from tissue cells (erythrocytes) by some proteolytic enzymes. Kellaway & Rawlinson (1944) describe the liberation of histamine from a cat's forelimb by perfusing at temperatures of 43–50° C.

From work in Oxford we now know that at least three other substances can enter the circulation after burning, viz. the nucleoprotein, the "pyronin" staining-substance and the proteinase, to these may be added the enzyme-hydrolysing tripeptide, which Zamecnik, Stephenson & Cope (1945) found in increased amount in lymph from the burned dog's limb and in human blister-fluid. One of these is perhaps the new protein described by Perlmann, Glenn & Kaufman (1943) in the lymph and serum from the burned limbs of calves, which migrated with half the speed of the globulin. With the slight reservation below, it seems certain that active proteinase escapes. Substances can certainly enter the circulation, on the other hand there is no evidence yet that these are in fact toxic. Miss Beloff and the writer have not been able to produce toxic signs in rats by injecting subcutaneously large doses of skin digest.¹

The fact that the proteinase must be liberated has led us to advance the hypothesis that the loosening of the tissue essential for the blister-formation is due to the enzyme's uncontrolled activity on its way from the tissue cell to the circulation. Medawar (1941) has already stated that digestion with trypsin of dermatome slices from human skin will separate sharply dermis from epidermis, as well as freeing individual cells from one another, this he believes is due to digestion of the elastin. Upon this whole question judgment should be suspended, our colleague, Mr. Leach, is now engaged upon a histological investigation covering this point.

In regard to the possibility that some of the disappearance of proteinase activity in the skin is due to entry of anti-proteinase, some relevant facts are now known. Direct trials of extracts of the skin show no activity of this kind, but plasma contains much antiproteinase for the skin proteinase, as little as 0.05 cm³ of plasma per cm³ of enzyme-extract is enough to inhibit the skin-proteinase activity to the extent of 70–80% (Beloff, unpublished observations). This means that proteinase reaching the circulation must soon be neutralized, which would explain the negative results found upon injection. It is of course most reasonable to think that the body would be able to protect itself against a large incursion of proteolytic enzyme from the tissues. Locally in the skin, matters will be complicated, escaping proteinase will meet at some point at present unknown anti-proteinase diffusing from the plasma.

⁹ [Beloff & Peters (1944, 1945)]
¹⁰ [Bergmann & Fruton (1944), Bergmann (1942)]

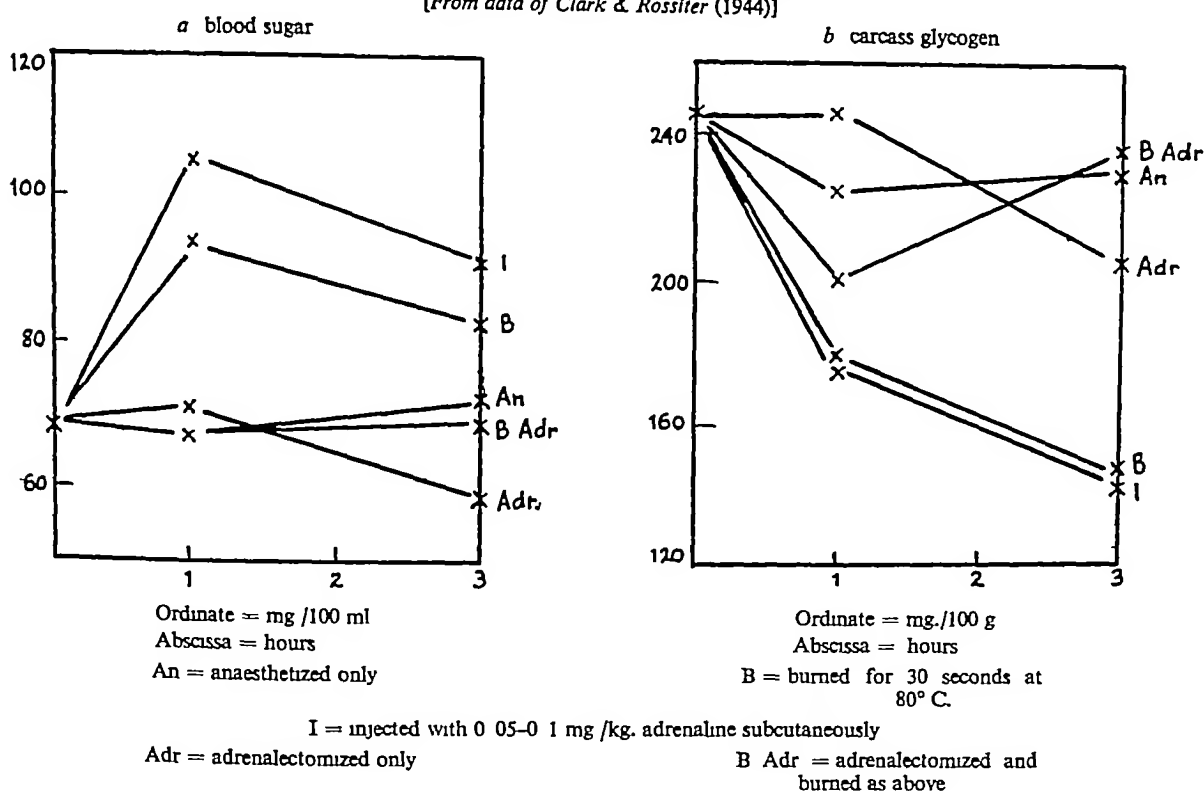
Systemic Effects of Burns

Like the stone in a pool, the local biochemical lesion spreads its influence in the system. Mention has been made earlier of the period of haemoconcentration lasting some 24 hours in the animal, and due to an altered capillary permeability which is local, associated with this period some marked changes occur in carbohydrate metabolism, Clark & Rossiter (1944) in this laboratory have recently put upon a secure basis the hyperglycaemia following burns, which is at a maximum in rabbits about 4 hours after burning (Fig 4a, 4b). In rats there was a similar increase in lactic acid and a fall in carcass glycogen, uninfluenced by previous ingestion of carbohydrate

course of the nitrogen excretion in rats (Clark, Peters & Rossiter, 1943). Some of these are shown in Fig 5. Coincident with "shock" there is a rise of the concentration of urea in the blood (azotaemia) and a fall in plasma protein, especially albumin, due to the leakage of a protein-rich fluid into the burned tissues. This is also seen in man.¹² Together with the early blood changes, there is a temporary rise in the output of urinary creatine. The early rise in weight due to tissue infiltration with water is followed by a weight loss, which tends to become more serious as the temperature of the burn is increased, showing that it is genuinely a "burn" effect. Loss in weight is accompanied by large losses of nitrogen as urea in the urine. Some apparently toxic effect therefore persists in animals long

FIG 4—CARBOHYDRATE METABOLISM IN BURNED RATS

[From data of Clark & Rossiter (1944)]



These changes were absent in adrenalectomized rats and could be mostly, though not entirely, imitated by injection of adrenalin. The condition approximated to that found in haemorrhagic hyperglycaemia. One new condition was found, there was less glycogen in the liver of the burned animal than in that from the adrenalectomized animal, further, slices of liver from the burned animal failed to synthesize glycogen from glucose *in vitro*. This change in the behaviour of glycogen was also coincident with the haemoconcentration period, it was not due to increased rate of breakdown of glycogen, to acidosis, or to an increase in the amount of serum amylase, at present its cause is unknown. Apart from the fluid loss in the tissues and haemoconcentration, there were no changes in the carbohydrate metabolism suggesting toxæmia. Taylor, Levenson & Adams (1944) have recently studied the carbohydrate metabolism of burned patients, and have recorded hyperglycaemia and lactic acidæmia.

Changes in Nitrogen Metabolism

The changes in nitrogen metabolism are more complex because they extend beyond the period of haemoconcentration. It has been known for long that loss of "nitrogen" occurred in burns (cf Lucido, 1940), and in 1941 Dr Black drew our attention to the urinary losses of nitrogen in one of his patients.¹¹ Preliminary studies upon loss of weight in rats after removal of skin were made by Barnes and Mansfield in 1941, and after burns in guinea-pigs by the writer in 1941-42. In 1943 we observed systematically the effects of graded temperature burns (¼ of body surface) on the behaviour of blood constituents and upon the subsequent

after the haemoconcentration has disappeared. It is an important point that Dr Vollum¹¹ can find no bacteria in the wounds in these animals. This shows that the N loss can exist apart from the bacterial toxins. Though azotaemia is known to follow dehydration (cf Black, 1942), there is no evidence that it will explain these persistent losses.

The metabolic effects found in patients can be reproduced in animals. During the course of our work, knowledge of these conditions in patients has been much extended, especially striking results were reported by Taylor, Levenson, Davidson, Browder & Lund (1943) in the U.S.A., who found a persistent azotaemia in their patients with large nitrogen losses, they had to give up to 2000 g. protein per week to produce positive nitrogen balances, similar results were reported by Anderson & Semonoff (1944) from Colebrook's team in Glasgow. Loss of protein through the skin in patients by oozing may amount to as much as 39 g. protein per diem.¹³ In controlled experiments upon rats burned at 73° C for 30 seconds (Croft & Peters, 1945a, 1945b) it was found that an addition of 8% casein to a diet containing 10% casein plus 10% yeast will abolish the urinary losses of N due to burning. These changes in N-excretion after burns are all reminiscent of the fundamental studies of Cuthbertson and colleagues upon the course of metabolism following fractures (Cuthbertson, 1930, 1942) indeed, in a document only recently seen by us, Cuthbertson independently in 1942 suggested feeding extra animal protein in the healing period of the burn to replace S-containing amino-acids lost from the skin, our own studies were planned early in 1941, but were delayed while the data on satisfactory

¹¹ [Taylor, Levenson, Davidson, Browder & Lund (1943)]

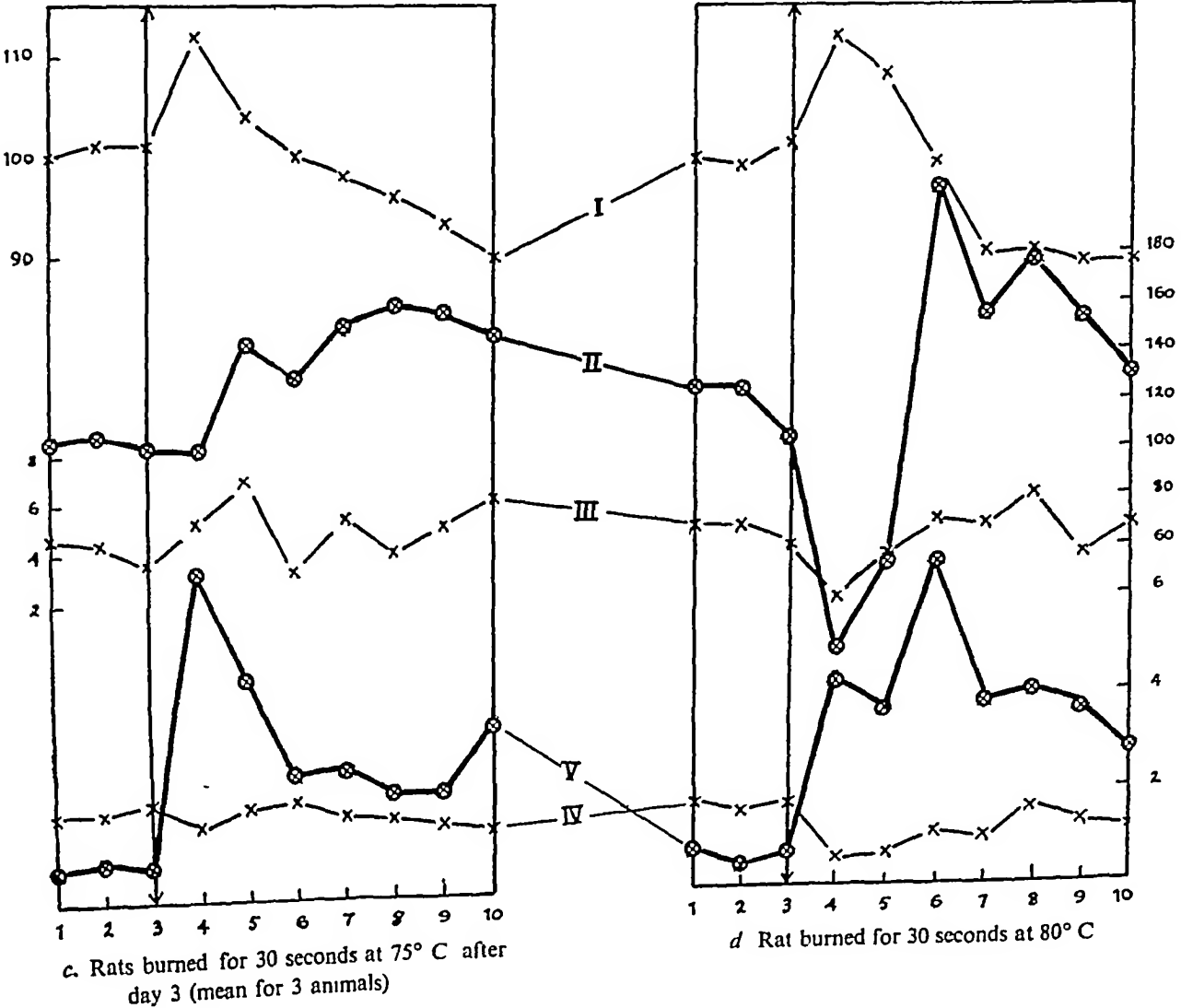
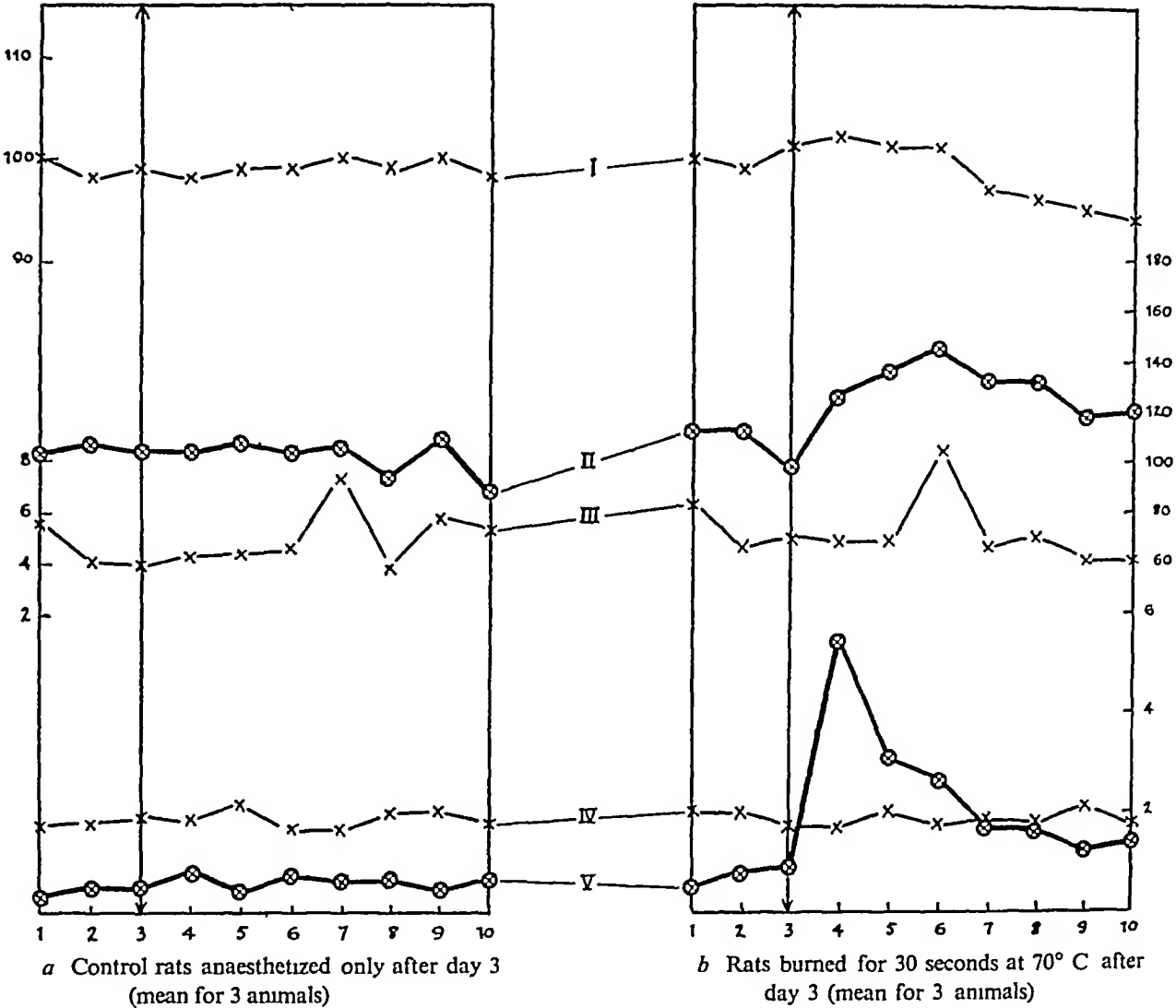
¹² [Hirschfeld, Williams, Abbott, Hiller & Pilling (1944)]

¹¹ [Personal communication]

FIG 5 —DAILY URINARY NITROGEN-EXCRETION OF RATS ALL FIGURES REFER TO A 100 g RAT

[From data supplied by Clark, Peters & Rossiter (1943)]

I = body-weight (g.)
II = urica (mg)
III = ammonia (mg)
IV = creatinine (mg)
V = creatine (mg)
Abscissae = days

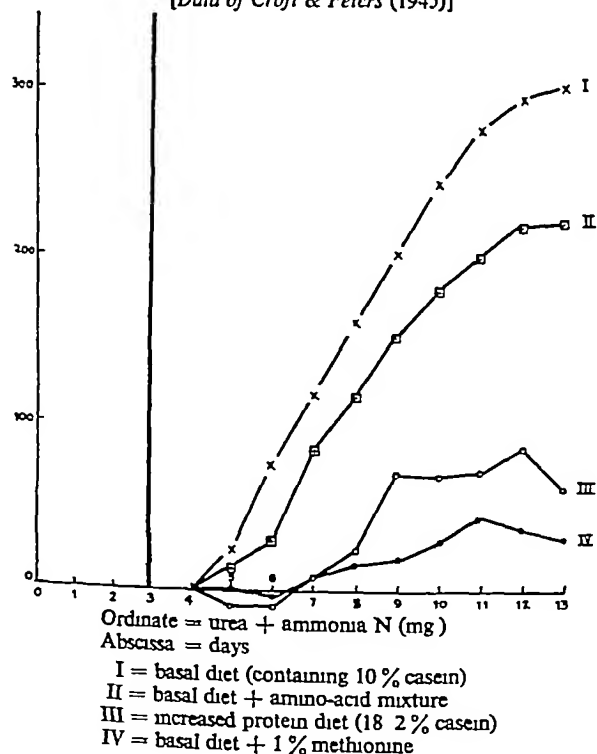


methods of producing experimental burns accumulated and until amino-acids became available

Our animal experiments have been extended to a study now in progress on the effect of individual amino acids upon the nitrogen loss after burning in rats. They were planned upon the hypothesis that the nitrogen loss is due to the raiding of the tissue stores of protein for one or more essential amino-acids, with the consequent elimination of the remaining N from other unwanted acids of the protein molecule. The most important amino-acid suggesting itself in this connection was methionine, discovered originally by Mueller (1923). In the spring of 1943, the writer was able to obtain the help of the Ministry of Supply in its manufacture. Much interesting modern work has stressed the functions of this amino-acid in serving as a source of cystine and of methyl groups.¹⁴ At present the results obtained with P. B. Croft show that supplements of methionine alone (1% of the diet) are much more effective in removing the negative N-balance than either alanine alone or an amino-acid mixture¹⁵ (Fig. 6).

FIG. 6—MEAN CUMULATIVE NITROGEN LOSS ON DIFFERENT DIETS FOLLOWING BURNS AT 73° C FOR 30 SECONDS

[Data of Croft & Peters (1945)]



It is curious that an amino-acid mixture containing as much methionine as that given in the addition of casein was ineffective, we have suggested that this is due to a slower rate of absorption when in association with the protein.

The value of methionine in these rat experiments both supports the hypothesis and justifies a clinical trial in the stages where a burned patient cannot get enough protein. Though not very palatable, methionine can be given by mouth, 5 g has been tolerated by jaundiced patients.¹⁶ Cysteine has not proved effective in reducing the N loss, this suggests at first sight that we are dealing with the well-known effect on the fat metabolism in liver and upon hepatic damage,¹⁷ but the matter is unsettled, as there is not much evidence now for liver-damage in burns.¹⁸

Summary of Findings

The nature of the biochemical lesion in the skin due to a thermal burn, and of its systemic effects, has been investigated in animals. 50–55° C for 30–60 seconds is a critical temperature for damage, producing permeability-changes, with liberation of substances from the skin-cells, which can be detected histologically. The degree of damage has been

correlated with increasing temperature. Higher temperatures induce a different condition, including fixation and coagulation of the protein, the actual temperature for damage is 48–50° C. This temperature can destroy some enzymes in a short period, but it is not yet decided whether enzyme-damage or change in lipoprotein in the cell interface is the initial biochemical alteration.

Many active enzymes can certainly leave the cells after exposure to the low temperatures producing burns. A new proteinase has been found in skin, and it can be liberated unchanged by burning, it is thought to be of significance in blister formation, and may be related to the appearance of histamine, owing to the activity of plasma "anti-proteinase," entry of some proteinase into the blood is evidently not normally dangerous. Tissue-infiltration of fluid into the skin occurs with great speed and can be prevented by pressures of no more than 10–20 mm Hg. The changes induced in the blood (haemoconcentration) by fluid loss into the burned tissue are accompanied by a hyperglycaemia and lactic acidemia, which are partly due to liberation of adrenaline, the liver also loses the power to synthesize glycogen from glucose.

Losses in body-weight and negative nitrogen balances extend beyond the haemoconcentration period, together with changes in N compounds in the blood, they are directly due to the burn, because they increase with the severity of the burn, though they simulate a toxic condition, they can be eliminated by increasing the amount of protein in the diet, further, the S-containing amino-acid methionine, given alone, will eliminate the losses of nitrogen as urea in burned rats, hence the toxemia appears to be a conditioned amino-acid deficiency induced by an increased demand for this amino-acid, with consequent raiding of the tissue-protein.

Though our work is not much more than the start of knowledge upon the local biochemical lesion and its "systemic" repercussions, it has provided some facts which must be thoroughly explored before it can be decided whether any local mitigation or reversal of some of the damage caused by a burn is possible.

The united effort of our team has not produced a "burn toxin," but the hypothesis of the toxin is useful, as its pursuit has brought to light new facts of theoretical as well as practical interest, among the latter are the two types of burn, the pressure for prevention of entry of fluid, the proteinase in relation to skin pathology in general, the changes in carbohydrate metabolism, and the later effects upon protein metabolism, with the possibility that extra carbohydrate may be of clinical value in the earliest stages and that single amino-acid therapy may replace protein, when appetite is too poor for the larger amounts of extra protein required to stop the negative N-balances.¹⁹

Note on Control of Infection²⁰

No statement upon the subject of burns should be made without some allusion to the importance of preventing the presence of bacteria in the wound, owing to the ease with which they can convert comparatively slight damage into something very serious. During the war, L. Colebrook and his team (Medical Research Council, 1944) have made a continuous study of treatment, at Glasgow especially. Improvements which have been made both in Britain and America, are (a) the insistence upon better sterility in first-aid treatment, (b) the cleansing with "cetavlon" (Barnes, 1943), (c) the use of sulphonamides and penicillin pastes.

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¹⁹ [This review deals mainly with our own work together with relevant reference. For general review of burns, see Harkins (1942), Rossiter (1943), Glenn (1944), and of N metabolism Cuthbertson (1945).]

²⁰ [In this connection, reference should be made to papers by F. H. K. Green in this number (BMB 690) and A. A. Miles in a preceding number (BMB 554)—Ed.]

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²¹ [BMB 719/127]

²² [BMB 711]

²³ [BMB 701]

²⁴ [BMB 702]

EXPERIMENTAL PATHOLOGY OF BURNS

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No more fitting introduction to a brief survey of the experimental pathology of burns can be made than by paying a much deferred tribute to the pioneer discoveries of a group of little-known British investigators. In modern times a somewhat grudging acknowledgment of the contributions of William Addison and Waller to the study of inflammation has been given, it is not generally appreciated how much is owed to other clinicians of the first half of the 19th century.

In his *Lectures on inflammation* (1813), John Thomson clearly described the more important responses of blood-vessels to strong irritants, including caustics, strong salts, acids and alkalis. By his use of transparent living tissues such as the frog's web, Thomson laid a firm foundation for experimental pathology.

Charles Hastings, in 1820, included amongst a variety of experiments on the web of the frog's foot the use of hot water, and noted that contraction of vessels and accelerated blood-flow quickly followed, to be replaced after a time by dilatation and retarded flow. Ice made such distended vessels contract, and reduced the circulation-rate. Hastings may be said to have initiated the experimental study of burns.

Similar methods, resulting in many new observations, were employed by Philip (1839), W Addison (1843), Travers (1844), Wharton Jones (1850) and Lord Lister (1857).

Addison heated the frog's web to 94° F [about 34.5° C] for 30 seconds and noted vascular changes identical with those following on a variety of injurious procedures. Wharton

Jones employed strong caustics, Lister high temperatures and chemicals. From these dynamic studies came a complete description of inflammation in general, and of the effects of thermal injury in particular. Modern work has added little of significance to such pioneer studies. Long before the modern era of experimental pathology was initiated by the brilliant contributions of Cohnheim, a complete and accurate appreciation of the local effects of thermal injury existed. This recognized a sequence of overlapping stages, started off by the action of heat, and quickly followed by damage or destruction of the tissues, and outpouring of fluid from the vessels of the heated area, somewhat later by migration—with increasing tempo—of colourless corpuscles from these vessels into the surrounding damaged parts, and eventually by a return to more or less normal conditions through repair of the affected parts.

Recent Studies on the Nature of Burns

In recent years a great deal of attention has been given to the problem of burns and various aspects have been re-studied in some detail, admittedly with practical questions of treatment given first place. In an attempt to decide what initiates the complicated process of burn-reaction, the action of graded temperatures on the skin has been reconsidered. Leach, Peters & Rossiter (1943) in a series of careful experiments with the guinea-pig, have shown that applications of 47° C for up to 6 minutes produce no visible change, but that

at 50°–55° C. for 1 minute and over there is a critical temperature for the development of permanent and irreversible damage. Scab-formation at this temperature indicates severe epidermal injury, whilst vascular disturbance is shown by the local oedema which sets in very quickly at 60° C, and may be detected even at 55° C.

Microscopical changes suggest two different types of heat-reaction. With milder burns there is cellular disintegration of affected areas, with more intense burns, there is heat-coagulation. Epithelium seems to lose basophilic granules from the cytoplasm and nucleoprotein from the nuclei. These two components have been identified in the inter-cellular blister-spaces, and their absorption may play some part in the production of systemic effects which follow severe burning. The dermis, too, is affected by more intense burns and collagen fibres become swollen and tend to dissociate into component fibrils, whilst their staining affinities alter and they take up basic dyes more avidly. Leach *et al* give useful figures for the development of oedema in burned areas, and show the rapidity with which this occurs, oedema may be present as early as 5 minutes after burning for 1 minute at 60° C.

This work serves as an excellent basis for correlation of macroscopic, microscopic and biochemical data and has a contribution to make in explaining the apparent dissimilarities in various types of burns. Rigid classifications may be misleading if they divert from fundamentals. Take for instance the grouping by Elman & Lischer (1944) of burns according to three grades of damage to the skin, those showing (i) oedema, produced by low temperatures or short exposure, (ii) wet necrosis, produced by medium temperatures and more exposure, (iii) dry necrosis, after higher temperatures and longer exposures. Such a classification may have some practical value in treatment, especially of infection, but anything which directs attention from the primary process should be regarded with caution. There is not the least doubt that necrosis, oedema and other vascular phenomena are common to all burns, although they may vary in their degree of development according to such factors as temperature of burning, duration of exposure, various obscurities in make-up of affected tissues and, no doubt, general constitutional factors.

The problem of greatest importance still seems to be the manner in which protoplasm responds to thermal injury, and the possibility of agents being evolved which will set in action the well-known reactive processes in the normal tissues around the burn. A little thought should suffice to convince one of this. The thermal bombardment of a tissue need last for a short time only, it ceases completely, yet there follows a regular chain of events which may extend over hours or days. It would appear, therefore, that something is liberated from the damaged cells—and, what is more important, continues to be liberated for a long time—which is responsible for the oedema, the leucocytic emigration and infiltration of the injured region, and later on the repair.

The Hypothetical "Burn Toxin"

No more valuable impetus to investigations of this sort has been given than that from the researches of the late Sir Thomas Lewis¹ and his school and more recently from Menkin. Lewis (1927) has suggested that traumatized tissue liberates histamine or histamine-like substances, which, in incredibly small amounts, call into being many of the features of inflammation. Menkin (1940) refers these to another product of damaged cells, leucotoxin. Recently Kellaway & Rawlinson (1944) have demonstrated that organs perfused with hot saline liberate a number of cell products, including histamine. Beloff & Peters (1944) also bring forward evidence that a proteinase may be liberated from rat's skin by burning and suggest that such an enzyme may prepare the skin for blister formation. It is possible that liberated enzymes may act as "burn toxins" when absorbed and cause a general toxæmia. Here is a field of fundamental enquiry which should give good returns in practical as well as purely scientific results.

Local Oedema in Burns

The most striking feature of a burn is the intense local oedema which sets in so rapidly. Within a few minutes of

burning, the water content of the affected area increases (Leach, Peters & Rossiter, 1943) and fluid continues to pour from the vessels for some time. A burnt limb steadily gains in weight (Harkins, 1942) and the composition of the blood in the hours succeeding extensive burning alters greatly (Underhill, Kapsinow & Fisk, 1930, Blalock, 1931, 1934, Harkins, 1942, Medical Research Council, 1944, Cameron, Allen, Coles & Rutland, 1945). It has been shown by numerous workers that the effusion into the burn is blood-plasma, as it has a high content of plasma protein, and its production is referred to increased permeability for colloids of capillaries, consequent upon the direct action of heat, or products of tissue-cells damaged by heat. Part of this fluid is removed by increased lymphatic flow (Glenn, Peterson & Drinker, 1942, Glenn, Muus & Drinker, 1943, Courtice, unpublished observation), but such lymphatic compensation is unimpressive quantitatively, and the local oedema seems to spread uninterruptedly until the capillaries recover and the supply of fluid ceases. It is possible that a certain amount of effused plasma returns to the circulation by way of the capillaries, though this is hindered by the high protein-content and the tendency for some of the intercellular fluid to coagulate.

Alterations in capillary permeability can be demonstrated at a very early stage after burning, by the use of colloidal dyes or suspensions of particles which do not leave normal vessels when they are introduced into the circulation (Cameron & Short, unpublished data). Within a few minutes of burning, whether thermal or chemical, such dyes can be traced through capillary or venous walls into the perivascular tissues. Macroscopic demonstration, too, is easy, the dye becoming localized around the affected region within 3–4 minutes of burning. This increased permeability of vessels is the key to all types of burns, no less than to other types of injury, with burning it takes on an added importance, as it develops at a truly remarkable speed and is responsible for immense losses of fluid from the blood, as well as localized blistering.

Blisters usually commence in the epidermis as small collections of fluid separating the prickle-cells from one another and from the deeper-lying cells (Leach, Peters & Rossiter, 1943). This is invariably the case with thermal, and also applies to some chemical, burns, in other instances, the whole of the epidermis may be lifted up uniformly from the dermis, as if the anchoring basement-membrane between dermis and epidermis had suddenly been loosened or destroyed. In either case, the basement-membrane plays an important part in blister-formation, yet surprisingly little information exists about its nature and the factors which control its adhesiveness. Peters' suggestion that skin proteinase may be responsible for the detachment of epidermis from dermis, in the way that Medawar (1941) has shown to exist with trypsin, should be extended to a study of the basement-membrane, and might well prove to be the solution of what has hitherto been a puzzle.

Countering Fluid-loss by Pressure

The importance of local fluid-loss from burning has been appreciated by surgeons and has led to the introduction of plasma- and fluid-administration on a generous scale (see Medical Research Council, 1944, for discussion). The application of local pressure to the burned region has also given beneficial results through the reduction of fluid-escape (Cope & Rhinelander, 1943, Rossiter, 1943, Rossiter & Peters, 1944, Cameron, Allen, Coles & Rutland, 1945). In a recent discussion of their experiments on goats, Cameron, Allen, Coles & Rutland have pointed out that present evidence suggests that pressure application (i) leads to reduction in burn-oedema (Barnes & Trueta, 1941, Glenn, Gilbert & Drinker, 1943, Rossiter & Peters, 1944, Cameron *et al.*, 1945), (ii) reduces fluid loss from the circulation, inhibiting haemoconcentration and restricting the loss of serum-protein (Siler & Reid, 1942, Lischer & Elman, 1943, Sellers & Willard, 1943, Sellers & Goranson, 1944, Cameron *et al.*, 1945), (iii) reduces the effects of increased capillary permeability in the burned area (Glenn *et al.*, 1943, Cameron *et al.*, 1945), (iv) reduces lymph flow (Barnes & Trueta, 1941, Glenn *et al.*, 1943), and (v) raises the subcutaneous tissue-pressure (Cameron *et al.*, 1945). Hence, pressure combats altered capillary permeability through increasing the tissue-pressure, local plasma-loss is reduced, plasma volume-decrease

¹ [Sir Thomas Lewis died on March 17, 1945.—Ed.]

is inhibited, and the main danger during the first stages after burning is lessened

Tissue-repair Local and Systemic Effects of Curative Agents

Repair of burns occurs in much the same sort of way as repair in wounds. Epithelial regeneration proceeds from the edge of the burn and from islets of retained epithelium on the bare surface. Cells migrate from these foci, later on proliferating and giving rise to the differentiated structures of epidermis. Dermis repair, too, presents no striking difference from that with any type of wound, and the usual stages are through formation of granulation-tissue and fibrosis with scarring. The problem is to deal with excessive necrotic tissue, which may hold up repair, and to prevent or eliminate infection.² Equally important, too, is the avoidance of methods of local treatment which add to the burden of the already heavily-taxed tissues. Experimentalists have done good service in studying the effects of curative agents on the initial burn-necrosis, and the response to these, as well as their action on healing. It has been shown that the much-favoured tannic acid may induce necrosis and delay healing (Cannon & Cope, 1943, Barnes & Rossiter, 1943, Cameron, Milton & Allen, 1943, Hirschfeld, Pilling & Maun, 1943, Ham, 1944, compare the clinical impression of Mowlem, 1941), and that the least toxic agents are the sulphonamides and penicillin, next in order of toxicity being the acridine salts, whilst propamidine and some of the acridine bases are definitely more toxic (Glynn, 1941, Selbie & McIntosh, 1943, Allen, Burgess & Cameron, 1944, Zintel, 1944). This list could be extended if space allowed. There is also the important matter of absorption of toxic substances from burns, a problem which has created a great deal of interest in the case of tannic acid (Wells, Humphrey & Coll, 1942, Erb, Morgan & Farmer, 1943, Robinson & Graessle, 1943, Barnes & Rossiter, 1943, Forbes & Evans, 1943, Cameron, Milton & Allen, 1943). It is sufficient to say that convincing evidence now exists, both from experimental and clinical sources, of the possibility of absorption in this manner of enough tannic acid to produce serious damage of the liver.

² [see BMB 690 & 554—Ed.]

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² [BMB 713]

³ [BMB 719/127]

⁴ [BMB 711]

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No discussion would be complete without mention of the general effects which so often prove serious when burns are widespread and deep. It must be admitted that the pathologist has contributed little to this admittedly difficult problem. Comprehensive surveys of necropsy-findings in fatal cases, such as those of Marchand (1908) and Pack (1926), give little lead in the search for the cause of the fatality, modern studies of this kind have also proved disappointing (Harkins, 1944, Cameron *et al.*, 1945). But what is clearly emerging from experimental studies is the importance of initial local fluid-loss, it is not too much to say that this is the key to the patient's condition during the first day or two after burning, and if it be prevented or inhibited, the outlook is good. Local fluid-loss leads to anhydraemia and haemoconcentration, the latter, if severe, places a serious strain upon the circulation which, if not corrected, may produce a fatal circulatory failure. Even if not fatal, after-effects may be formidable, especially when the renal blood-flow is considerably reduced during the anhydraemic phase. One can be easily convinced of the importance of haemoconcentration in the absence of any other complicating factor, by carrying out the experiment of introducing large amounts of hypertonic glucose solution into the limbs of an animal. In recent unpublished experiments of this kind, the writer and his colleagues have produced most of the general pathological features of the early stages of severe burning, and have shown that local fluid-loss around the site of injection of such a hypertonic solution is sufficient to produce a degree of haemoconcentration similar to, and as serious as, that seen after extensive burning. There would appear to be little reason for postulating hypothetical toxins at this stage.

Later on, when the burnt tissue breaks down, there is more reason to suspect the action of toxins, though here again caution must be exerted, as secondary infection often supervenes. The experiments of Florey and his colleagues (Abraham, Brown, Chain, Florey, Gardner & Sanders, 1941) suggest that large amounts of necrotic tissue are tolerated by the organism, provided that infection is not implanted in such a nidus. All theories of "shock" production, toxæmia, and the like, should at present be regarded with reserve if secondary infection is present.

THE LOCAL TREATMENT OF THERMAL BURNS

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"Over one thousand papers dealing with burns have been listed in the *Quarterly Cumulative Index Medicus* during the past decade, and the number is increasing rapidly under the stimulus of the high incidence of thermal burns in the present war." Thus begins an authoritative American review of the local treatment of skin burns, published last year (*Journal of the American Medical Association*, 1944), and the figure, though to some it may seem staggering, will be hardly surprising to anyone who has attempted to follow the flow of publications on this contentious subject, even in the English-speaking countries during the war years. One of the chief reasons for the multiplicity of publications on burns is undoubtedly the failure of many authors to realize that superficial blister-burns of extent too small to cause systemic disturbance will heal rapidly of their own accord under any treatment which protects them from infection and does not itself interfere with the natural processes of skin repair. accurately controlled experiments on human burns being virtually impossible, there has been a tendency to acclaim as triumphs of therapy with particular methods, rates of healing which might equally have been attained with other methods—or, indeed, with no method at all, apart from covering the area of damaged skin against the risks of bacterial invasion from the environment, and of further injury.

Pathology of Burns

A classification of skin burns which has been widely adopted in recent years divides them into three degrees of depth only, instead of the six propounded by Dupuytren.

First degree burns are those involving only the most superficial layers of the skin, producing simple erythema and slight oedema, due probably to the local release of a vasodilator substance, as the epidermis is not penetrated, the risk of infection is negligible, and these burns, though initially painful, usually recover rapidly with any treatment or without treatment, they do not cause systemic effects unless they are very extensive.

Second degree burns are characterized by blistering, they involve a varying thickness of the skin, but always leave intact either a complete layer of deep epithelium beneath the blister, or at least some epithelial islets, notably around undestroyed sweat glands and hair follicles, from which—in the absence of further damage due to infection, misguided therapy, or renewed trauma—epithelial regeneration can spontaneously occur. These burns uncover nerve-endings, and tend to be very painful so long as they are exposed to the air. Moreover, they are associated with damage to the blood-vessels in the corium, leading to increased capillary permeability in and around the injured area—with its sequels of local swelling, "weeping" from the burned surface, and, if the burns are extensive, sufficient loss of plasma from the circulation to produce the well-known phenomena of "burns shock."

Third degree burns involve destruction of the full thickness of the skin, but as the epithelium of the sweat glands and hair follicles extends into the subcutaneous tissues, some amount of epithelial regeneration is possible even in areas of third-degree burning, unless the sweat glands and hair follicles are completely destroyed, apart from regeneration from such surviving islets, spontaneous epithelial repair of third-degree burns can take place only from the edges, after separation by sloughing of the heat-coagulated tissues, and the slow growth of granulation tissue to fill the gap, such burns therefore always require skin-grafting to secure rapid healing of even moderate-sized areas. Because the nerve-endings in third-degree burns are destroyed rather than exposed, these burns tend to be less painful than those of second degree. It will be realized, however, that, except in the case of strictly localized injuries, such as those sometimes caused by electrical currents or by hot metal, it is rare for a patient to sustain third-degree burns without a surrounding area of second-degree damage, and it is often impossible for a week or more after burning to decide the true depth of the tissue-destruction in a given area. The exposed tissues in both second- and

third-degree burns are very liable to infection, especially—in the early stages—by the haemolytic streptococcus, which may be conveyed to the burn from the air, from dust, from the use of unsterilized blankets, and from the throats and noses of the patient or his attendants. Such infection may itself increase the depth of tissue-damage, it may imperil life, and—particularly in third-degree burns involving muscles or tendons, for example, in the hand—it may lead to crippling deformity due to the excessive formation of scar-tissue, and to its subsequent contraction.

The risk of loss of plasma into the tissues around the injured area, with the resulting production of "burns shock," is probably at least as great with third-degree burns as with those of second degree, though the loss of fluid by "weeping" from the surface is less with the former, owing to the heat-coagulation of the superficial layers. It is likely that the presence of extravasated protein-fluid in the tissues around a burn itself assists the formation of excessive scar-tissue, by providing a favourable medium for the proliferation of fibroblasts (Glenn, Gilbert & Drinker, 1943).

No decision has yet been reached on the controversial question whether there is a non-bacterial "toxaemia of burns," due to the absorption of endogenous poisons derived from the damaged tissues. Peters and his group at Oxford have been working on this problem during the war, and there have been somewhat similar investigations in America. It is possible that enzymes or other substances liberated from the tissues damaged but not coagulated by heat, towards the periphery of a severe burn, may themselves act as systemic poisons, but the question is still open. It is ironical to reflect that the widespread belief in this form of toxaemia before the war was one of the reasons for the popularity of tannic-acid treatment (which was thought to "fix" the endogenous toxins), for it is now known that the absorption of tannic acid applied to extensive or deep burns may itself cause an undoubted "toxaemia," associated with necrotic changes in the liver (Wells, Humphrey & Coll, 1942, Wilson, 1942, Erb, Morgan & Farmer, 1943, Cameron, Milton & Allen, 1943, Barnes & Rossiter, 1943, Hartman & Romance, 1943, and many other authors). Its toxic action when absorbed is the chief of several unfavourable features which have led since 1940 to the almost complete abandonment by British and American workers of tannic acid for the treatment of burns.

In the later, "sloughing" and granulating, stages of deep burns, mixed infection by a variety of bacteria is frequent. Some of these organisms—e.g., *Proteus*, *Ps. pyocyanea*—are very resistant to bacteriostatic and bactericidal agents, including the sulphonamides and penicillin. Although, in the opinion of many authors, the presence of *Proteus* or *Ps. pyocyanea* in a burn need not itself delay attempts at skin-grafting with patch grafts, it is likely to reduce the chances of "100 per cent. take." Moreover, the occurrence of mixed pyogenic infections in burns is one of the causes of the protein deficiency, anaemia and cachexia which may kill severely-burned patients who have survived the still more dangerous, earlier condition of "burns shock." There is no doubt that an efficient method of controlling such resistant infections in the sloughing and granulating stages is one of the outstanding needs of burns therapy to-day.

Aims of Treatment

After this brief review of the local pathology of burns, it may be helpful to set out the chief aims of treatment at the different stages, and then to consider how far these are met by some of the principal methods in current use. No attempt will be made to survey all the different procedures recommended in recent years that would not be possible in the space available. Following Colebrook and colleagues (Colebrook, Gibson & Todd, 1944, Medical Research Council, 1944), the term "plenary treatment," suggested by Sir Alnroth Wright, will be used to denote the first surgical cleansing and dressing of a burn under hospital conditions.

The primary objectives in treating burns are to save life, to prevent or combat infection, to maintain and restore

function, and to restore appearance, these may be amplified, on a chronological basis, as suggested in the Table

TABLE
OBJECTIVES IN THE TREATMENT OF BURNS

1 To relieve pain,	Immediate Treatment (in- cluding first- aid, where applicable, see below)	
2 To prevent invasion of the raw surface by pathogenic bacteria—in particular, haemolytic streptococci,		
3 To do no further injury to skin tissues which, though damaged, may still be viable, and not to interfere with the natural antibacterial defence by leucocytes,		
4 To prevent or minimize plasma-loss into the tissues around a burn, and from the raw surface,		
5. To counter "burns shock," by (a) morphine (where pain is severe), (b) moderate (but not excessive) environmental warmth, (c) fluids by the mouth (when they can be taken), and (d) adequate intravenous "replacement therapy" with plasma or serum		
To attend thereafter to the correction of the metabolic disturbances which follow burning, by prescribing appropriate diet, etc.,		
6 To prevent the risk of infection or reinfection of the burns in hospital,		
7 To eliminate pathogenic organisms already present on the burned area and surrounding skin, without doing further injury to viable tissues ("plenary treatment"),		
8 To control local oedema around the burn,		
9 To maintain free movement of joints in the neighbourhood of burns (e.g. those of the fingers where the hands are burned),		
10 To prepare the burned area for skin-grafting as soon as possible, unless the burns are so small, and so situated, that satisfactory natural healing within 21 days can be expected,	Early hospital treatment	
11 To assist the separation of sloughs, and treat streptococcal or other infections which may be delaying skin-grafting,		
12. To treat the protein-deficiency, anaemia and cachexia which may follow severe burns, especially if they are heavily infected in the sloughing stage,		
13 To ensure satisfactory rehabilitation of the patient, and provide any necessary follow-up treatment, including x-ray therapy for keloids and plastic surgery to restore function and appearance.	Later hospital treatment	

First-aid Treatment

It is now widely accepted that wherever it is possible for a patient with extensive burns to be taken immediately to hospital, the best first-aid treatment of the burned areas is none at all, apart from covering any exposed burns with sterilized or recently-laundered cloths or towels, to protect them from air-borne infection. This should certainly be the rule, where practicable, in cases of burns involving more than 5% of the body-surface (the approximate skin area of both hands in an adult). As it is known that loss of plasma into the tissues around a burn begins within an hour of the injury, there would be theoretical advantages in applying pressure and postural treatment at this stage, to control the local oedema, but the satisfactory application of "pressure dressings" (see under *Hospital Treatment*, below) is liable to be difficult and time-consuming, and the efforts of the first-aid worker to this end might too easily be harmful, both by constricting the local circulation, and by increasing the opportunities for air-borne infection and for the development of "burns shock". Pain, if severe, should be relieved as soon as possible by morphine, and the patient should be wrapped up warmly for his journey to hospital, care being taken that unsterilized blankets—a rich source of streptococcal cross-infection—do not come into contact with the burns. Clothing, even if severely damaged, should not be removed, and no attempt should be made by first-aid workers to cleanse thermal burns, or the surrounding skin. Speed in transferring the patient to hospital, with a minimum of preliminary interference, is the guiding first-aid principle where conditions permit.

There are, of course, many circumstances, particularly in war, in which it is impossible for patients even with severe burns to be taken to hospital at once, and for these cases—and for patients with minor burns, involving no risk to life—

numerous widely differing schemes of immediate treatment have been suggested. The problem of devising a simple first-aid procedure of general applicability under these conditions was investigated by Colebrook and his colleagues at the Royal Infirmary, Glasgow, in 1942–43, as part of a large-scale study of the treatment of burns, initiated by the Medical Research Council (1944), their work led to the recommendation of the following formula ("No 9 Cream"), as a first aid application which has the important advantages of being bland, antiseptic, and easily removable for the plenary treatment in hospital (Colebrook, 1944; Colebrook *et al*, 1944, Medical Research Council, 1944)

Cetyl trimethyl ammonium bromide ("Cetavlon")	10 g.
Sulphanilamide	30 g.
Castor oil	250 g.
Beeswax	18 g.
Wool fat	18 g.
Cetyl alcohol	50 g.
Glycerin	100 g.
Water	524 g.
	1000 g.

Preparation Melt the castor oil, beeswax and cetyl alcohol at as low a temperature as possible. Dissolve the "cetavlon" in the water with the aid of heat, mix with the oil, etc., at about 60°C., and stir until set. The sulphanilamide is rubbed up with the glycerin, and then incorporated in the cream and thoroughly mixed, preferably with the aid of a Peerless Mixer, with the bent arm at slow speed. The cream cannot be heat-sterilized, but it can be regarded as self-sterilizing for the ordinary non-spore pathogens. It may be preserved for long periods by the addition of 0.2% chlorocresol.

The cream should be applied with a knife-blade or spoon, previously sterilized by dipping for 2 minutes in boiling water. It should be freely smeared over the burned area and surrounding skin. The burn should not previously be washed, nor should blisters be opened. After application of this cream, the burned area should be covered with sterile lint or gauze, firmly bandaged in place over layers of wool where practicable. Both the "cetavlon" and the sulphanilamide are of value in restraining the multiplication of haemolytic streptococci in the burn, but the authors emphasize the importance of observing due aseptic precautions in applying this or any other first-aid treatment to burns, so as to minimize the risk of conveying pathogenic bacteria to the raw areas. Thus, the operator's hands must be thoroughly washed and dried, and he should wear a gauze-mask or a clean handkerchief over his mouth and nose. This conception that the first-aid worker treating burns should, when possible, "dress up like a surgeon" is relatively new, but its importance has been shown by recent work on the methods of spread of "cross-infection".¹

As the "No 9 Cream" has been known very occasionally to cause dermatitis in susceptible subjects, Colebrook *et al* advise that it should not usually be left in contact with the burn for more than two days, in special circumstances, however, such as the treatment of burned patients in small ships or in ships' lifeboats, they point out that this risk may be ignored, as it is of small account compared with that of infection if the burn is not treated. That the risk of dermatitis due to "No 9 Cream" is extremely slight is indicated by the experience of Bodenham (personal communication), who has used it at an R.A.F. hospital for 3 years without encountering ill-effects, even when the cream has been left in contact with the skin for 5–7 days.

The workers at Glasgow investigated the desirability of adding local analgesic drugs to first-aid preparations for burns but, after careful tests, they advise against this, for the following reasons:

a The application of a local analgesic is unlikely to give sufficient relief for a severe burn, which will usually require morphine;

b The pain of many small burns is so transient as to need no analgesic;

c The relief of pain by local analgesics is uncertain and often short-lived;

d There is some risk of toxic effects from the use of local analgesics on a large burned area.

¹ [Also described as "hospital infection," "nosocomial infection" and "added infection." This subject has been fully considered in papers by Dr R. Cruickshank (*BMB* 553) and Prof A. A. Miles (*BMB* 554)—Ed.]

Most British and American authors seem to agree with these views, but the Germans are understood to use preparations containing benzocaine for the first-aid treatment of small burns, and amyl salicylate has been recommended for its analgesic properties in minor heat-burns (Stewart, 1937), as well as officially for burns due to vesicants, amyl salicylate has many disadvantages, including its extraordinarily penetrating smell, its feeble antiseptic power and the fact that it is not easily removable for plenary treatment, its use for thermal burns should be restricted to the small "domestic" or industrial injury where pain is the chief problem

As exposure to the air is an important factor in making a burn painful, it is usual for burned patients to obtain considerable relief as soon as their injuries are covered. This is recognized in the ingenious method adopted in the Royal Air Force for the immediate treatment of burns of the hands in aircrew on operational duties (Hudson, 1943, Air Ministry, 1944). The first-aid kit provided includes sets of Stannard "burn mittens," made of a transparent coated-silk fabric, which can be put on without difficulty, even by a man with severely burned hands. The mittens represent a special development of the Bunyan-Stannard coated-silk bag or envelope, which also has its uses in the treatment of burns—in the early stages, chiefly as a cover for burns in situations where satisfactory bandaging is impossible, and, in the later stages, mainly as a means of applying irrigation treatment to septic burns (Bunyan, 1940, 1941, Hudson, 1941, Pearson, Lewis & Niven, 1941, Hannay, 1941, Osborne, 1944, Goldberg, 1944). [Transparent jackets of various types, for the treatment of burns by irrigation and other means, had been used since 1935 by B. Douglas in America (see Douglas, 1944).] The Stannard first-aid burn mittens not only allow a sufficient range of movement for the injured fingers, but they contain a sulphonamide powder, which the patient, merely by raising and shaking them after he has put them on, is enabled to apply to his burns.

The application of sulphanilamide powder, covered usually by paraffined ("vaseline") gauze, has been widely recommended as a first-aid treatment by medical officers in the Fighting Services, but it is now known to carry the risk of a dangerous degree of absorption of sulphanilamide, where the burns treated are extensive (Gordon & Bowers, 1942, Medical Research Council, 1944). It is likely to be more and more superseded by the use of creams, such as the "No. 9 Cream" above or the sulphathiazole ointment recommended by Jenkins, Allen, Owens, Schafer & Dragstedt (1945), which contain not more than 5% of sulphonamide, and are thus free from this danger. Moreover, the use of sulphonamide creams may well be superseded by the introduction of penicillin preparations for the first-aid treatment of burns, if it is possible to find means of increasing the stability of these products, and of including with the penicillin an antibacterial agent with better effect against the Gram-negative organisms. Publications on the use of penicillin in the early treatment of burns have so far been scanty.

Only brief reference can be made here to certain other methods of first-aid treatment which have also given good service under appropriate conditions. Among these are the application of 1% gentian violet jelly or "triple-dye" jelly (gentian violet 1%, brilliant green 0.1%, eufлавine 0.1%, in a water-soluble base, with or without 5% of a sulphonamide), these applications are stated by Wakeley (1943) to have proved very useful in small ships carrying no medical officer, but they have the disadvantage of being tissue poisons and less readily removable than water-miscible creams for the plenary cleansing in hospital.

Hospital Treatment

The distinction made here between "first-aid" and "hospital" or "plenary" treatment is based on the assumption that a patient with extensive burns will receive first-aid treatment of his injuries only when it is impossible for him to be taken immediately to hospital, and that first-aid will otherwise be applied only to burns too slight to require in-patient treatment at a hospital. It frequently happens, of course, that a burned patient receives his first local treatment in hospital, and in such cases the division between "first-aid" and "plenary" treatment disappears. It is proposed first to consider under "hospital" treatment the various methods recommended for limiting loss of plasma by the

application of "pressure" to the burned surfaces and surrounding tissues although, as already pointed out, there is evidence that these methods, to be really effective, should be applied within an hour of burning, which brings them chronologically well within the range of "first-aid" procedures. They mostly, however, lack the technical simplicity desirable in a method intended for use by inexperienced personnel.

The "pressure dressing" method, much favoured in America, is simple enough in its fundamentals, but the dressings, in many anatomical situations, are difficult to apply satisfactorily. Good accounts of this method have been published by Allen & Koch (1942), Siler (1944) and Koch (1944). These authors emphasize that its use should be preceded or accompanied by appropriate treatment for "burns shock," and that it should be carried out with full aseptic precautions. There is some disagreement between authorities as to whether the burns should be cleansed before the pressure dressings are applied, and, if so, whether anaesthesia is necessary for the cleansing. Koch and Siler stress that any such cleansing must be gentle, and that only non-irritant cleansers, such as plain white soap, warm water and saline solution, should be used. Siler recommends that blisters should be opened, but Koch considers this unnecessary. "most of them will probably give way under a well applied compression dressing." The burns are then dressed with sheets of gauze impregnated with a non-adherent preparation such as sterile soft paraffin or hydrous wool fat. A preparation of zinc peroxide has recently been tried as an alternative, to limit infection (Koch, 1944), and in the case of patients from the Coconut Grove night-club fire treated at the Massachusetts General Hospital, the preparation applied was boric ointment, without preliminary cleansing (Cope, 1943), it is recognized, however, that there is a danger of toxic absorption if boric acid is applied to extensive burns. At the Montreal General Hospital, a 5% emulsion of sulphathiazole with triethanolamine as a wetting agent, is favoured (Ackman & Wilson, 1942, Gurd & Gerrie, 1944, Cochran, 1944).

The non-adherent dressing, whatever its nature, should be covered with sufficient gauze and cotton waste to make it possible to effect firm compression of the whole injured area and its immediate surroundings by careful bandaging. Crêpe bandages are very useful in applying pressure-dressings, and also in preventing displacement of their dressings by young children. Elevation of the injured part on splints, where possible, brings the aid of gravity to the return-circulation, and helps to prevent stasis and discomfort, as well as ensuring rest, it is specially important in the treatment of burns of the hands. In the absence of evidence of infection, the initial pressure dressings may be left in place for up to 14 days, by the end of which time the burned areas will usually be completely healed wherever there has not been full-thickness destruction of skin. The same method is claimed to favour separation of the destroyed tissue if whole-thickness skin-destruction has taken place, thus making possible early skin-cover by grafting.

Most American surgeons who recommend the pressure-dressings technique now seem to prefer the systemic administration of penicillin or sulphadiazine to the local use of antibacterial preparations on the burns. In this, there is some divergence of opinion between American authorities and investigators in Britain (e.g. the group who carried out the work on burns at Glasgow).

The pressure-dressings method takes full cognizance of the principle, widely accepted in the present war as important in the treatment of burns and wounds, that the exposure of injured tissues for dressing purposes should be as infrequent as possible. A logical development both of this principle and of the pressure theory in the control of plasma-loss, was the use of closed plaster to treat limb-burns (Barnes, 1943). There has been considerable experimental work to show that the early and skilful application of plaster to burned limbs, combined with elevation to minimize reactionary oedema, does indeed control plasma-loss and reduce the fatality-rate from "burns shock" in animals (Sellers & Goranson, 1944, Glenn, 1944, Alinch & Lehman, 1944, Cameron, Allen, Coles & Rutland, 1945, and others). The method, however, has not so far found wide favour in human surgery, as there are many dangers unless it is very carefully applied, and many authorities hold that the degree of immobilization of joints thus provided is very undesirable, especially in the case of burned fingers.

Only brief reference can be made here to the many different forms of occlusive membranes which have been recommended for application to burns—to inhibit, at any rate, the loss of plasma from the surface. That most hallowed by usage is coagulation or “tanning” with silver nitrate, which is still favoured by some surgeons, as a less dangerous variant of the tannic-acid treatment, now largely discredited (Department of Health for Scotland, 1943). “Triple-dye” (see under *First-aid Treatment*, above) is sometimes used similarly. It is generally recommended that these methods should be preceded by thorough cleansing of the burns under anaesthesia, since the development of infection beneath the coagulum is the chief danger.

More recent types of occlusive preparation include films containing sulphonamides with various plasticizers—e.g. the Pickrell spray of sulphadiazine with triethanolamine, methyl cellulose and other substances (Pickrell, 1942). They may be combined with the use of pressure dressings. Some of these preparations—for example, the “sulfafilms” tested by Dingwall & Andrus (1944) and medicated “cellophane” as used by Farr (1944) and others—have at least the theoretical advantage of transparency, so that it is “possible to see what is happening beneath them,” but they also have their dangers. A paraffin-wax spray has been used as a bland, inert occlusive dressing, even for first-aid treatment, and a medicated gelatin film has been tested experimentally (Roback & Ivy, 1944). It was natural, too, that the question of covering burns with coagulated plasma or serum as a “physiological dressing” should be considered, and the possibilities of treatment of this type have been investigated by Macfarlane (1943), Miscall & Joyner (1944) and Rabinowitz & Perner (1944). Thin sheets of dried plasma containing sulphonamides have been similarly tried by Pollock (1944). Such treatment seems likely, however, to have only a limited range of usefulness. As an alternative to the use of blood-products, films containing casein have been tried by Curtis & Brewer (1944).

With most of the methods of local treatment discussed above, chief emphasis is laid on the prevention of loss of plasma from the circulation, and on the provision of temporary cover for the burns. In the plenary treatment recommended by Colebrook *et al* (Medical Research Council, 1944), greater attention is paid to the elimination of haemolytic streptococci which may already have reached the injured tissues. All important recent publications on the treatment of severely burned patients stress the necessity for early, and carefully controlled, plasma (or serum) infusion, but where the restriction of fluid loss by “pressure” is aimed at, the factor makes it desirable for the local treatment to chronize as nearly as possible with the urgent systemic treatment for “shock”, they should “go hand in hand,” as Koch says. In contrast, the Glasgow workers, though they applied their first-aid and plenary dressings with moderate pressure, relied much less on this than on the plasma infusions to prevent “shock,” and indeed their experience showed that where a preparation such as the “No. 9 Cream” had been used in first-aid, it was often better to postpone plenary treatment in the severely-burned patient until the second or third day after admission to hospital, so as to allow time for “burns shock” to be countered by adequate plasma (or serum) therapy beforehand.

At Glasgow and at the recently established Burns Unit at the Birmingham Accident Hospital and Rehabilitation Centre, the plenary cleansing of the burns and surrounding skin has been done, under very strict aseptic precautions, with a 1% “cetavlon” solution (Barnes, 1942, Medical Research Council, 1944, Colebrook, 1945), and it has been found that anaesthesia is usually unnecessary, except in young children. At this stage, blisters may be opened (with sterile scissors), and loosened epithelium removed. Each area is then dressed with a bland antiseptic cream, the following formula was used successfully in a large series of patients at Glasgow.

Sulphanilamide	3 g
Sulphathiazole	3 g
Glycerin	10 g
Castor oil	25 g
Lanette wax SX	10 g
Water	49 g
	—
	100 g.

Preparation. Heat 25 g of castor oil to 70° C and add 10 g. of Lanette wax SX. When the wax is completely melted, add water (49 cm³, previously heated to 65° C), with gentle stirring to avoid incorporation of air. Heat the whole to 100° C for at least 30 minutes, to kill non-sporing pathogens, and shake as it cools. Rub up the sterile sulphanilamide and sulphathiazole powders, 3 g of each, in a sterile mortar with 10 g of glycerin. Heat to 65° C for 2 hours and then mix slowly with the base. Store in a sterilized jar and keep always covered.

More recently, at Birmingham, a cream containing 3% of sulphathiazole and 200 units of penicillin per gram has been tried instead. Either preparation may be applied to the burns on sheets of gauze, and firm pressure is then secured by means of crêpe bandages over a heaped dressing of gauze and wool. Burned limbs are thereafter raised well above the heart level, so as to minimize local swelling. Unless there are clinical indications for removing the dressing earlier, it may be left in position for 6–12 days, depending on the site of the burn and the degree of comfort experienced by the patient, sites requiring earlier change of dressing are the hands (see below) and the areas around the mouth and nose, or the perineum and buttocks, where some degree of contamination is inevitable. On removal of the dressing from sites where it has remained satisfactorily for a week or more, many second-degree burns will be found to have healed, but the cream may be reapplied, without further washing but with rigid aseptic precautions, for another week if necessary. A special Dressing Station, supplied with filtered air to reduce the risk of hospital cross-infection, is used for re-dressing burns at the Birmingham Unit (Colebrook, 1945).

In the case of burns of the hand, where recovery of mobility is so important, experience at R A F hospitals indicates that after 3 or 4 days of treatment with a sulphonamide cream as used at Glasgow, it is better to remove the dressings and treat the injuries by immersion once to thrice daily in a bath of 0.9% sodium-chloride solution at about 100° F [38° C], the patient being encouraged to exercise his fingers in the bath. Between the baths, sulphanilamide powder and soft paraffin mesh (“tulle gras”) may be applied, the hand being elevated on light splints in the “basic functional position” of partial dorsi-flexion at the wrist, with semi-flexion at all finger joints, and apposition of the thumb and index finger tips, the risk of a toxic degree of absorption of sulphanilamide from burns affecting only the hands is relatively small, but the treatment should be controlled, where possible, by estimations of the sulphonamide content of the blood. All but the slightest burns of the hands should be skin-grafted as soon as they are ready (Jayes, 1944).

Saline baths are of value also in removing dressings from burns of the perineum and buttocks, where they are apt to adhere to the exposed tissues, and these baths have been used successfully in the treatment of septic burns, to assist the separation of sloughs, hot saline packs may be used similarly.

Where, after 6–12 days’ treatment with a sulphonamide preparation, a burn still shows clinical and bacteriological evidence of streptococcal infection, it is unlikely that further treatment with sulphonamides will be useful. In these cases, and in cases of staphylococcal infection, it is better to change to penicillin, if available, or to propamidine (McIndoe & Tilley, 1943, Clark, Colebrook, Gibson, Thomson & Foster, 1943). Good results in the treatment of infected burns with penicillin preparations have been published by Clark *et al* (1943), Bodenham (1943a) and others, and further experience of the use of penicillin to treat burns is accumulating. Unfortunately, this drug has little action against the coliform bacilli, *Proteus* and *Ps. pyocyanea* which—mainly as a result of hospital cross-infection—too often infect burns in the sloughing stage. The best way of dealing with this type of mixed infection is undoubtedly to prevent it, by a meticulously aseptic dressing technique. When it develops in spite of such precautions, it raises a difficult problem in therapy, since there is at present no antiseptic drug which is completely effective against these bacteria, in concentrations which will not damage the tissues.

In the view of many authors, results as satisfactory as any in treating such infections, and in assisting separation of the sloughs, are given by the use of chlorine antiseptics (e.g. Dakin’s solution, “euso” or “milton”), either on dressings kept moist with the solution by periodical irrigation through Carrel-Dakin tubes, or by direct irrigation of the burn in a “jacket” or “envelope” as recommended by Douglas and

by Bunyan. Slow separation of the sloughs from infected burns is one of the major factors in delaying skin grafting, and attempts have often been made to accelerate this process by the local application of proteolytic ferments (trypsin, papain), pyruvic acid has also been tried for the purpose in America, but the use of this substance is still in the experimental stage. Another factor hindering early skin-grafting is the presence in a third-degree burn of a dense mass of coagulated tissue. The possibility of preparing quickly for skin grafting by performing primary excision of deep burns of limited extent, such as electrical burns, always deserves consideration (Wakeley, 1941)

As the formation of granulation tissue is apt to be slow and deficient in patients with hypoproteinaemia, the giving of a diet rich in protein is an important ancillary to the local treatment of severe, extensive burns *

The writer is aware that from this necessarily cursory review of the local treatment of heat burns, there are many obvious omissions. There are numerous other forms of local treatment which appear to have given good results in the hands of their advocates, but to which it has not been possible to refer here, nor has it been possible to consider the late treatment and rehabilitation of burned patients (Bodenham, 1943b; McIndoe, 1943, Wakeley, 1942). There are, moreover, the peculiar problems of burns in special sites, such as the eyes, and space has not permitted a discussion of these. It may be thought by some readers that too much detail has been given about the methods used at the Royal Infirmary,

Glasgow, and the "pressure dressings" technique, and that some of this space might have been devoted to a short survey of the use of amino-acridine antiseptics in burns, and of methods intended to accelerate natural healing. The writer, however, is unrepentant on these scores, the use of amino-acridines is a treatment of many years' standing which is showing some signs of a revival in modified form (see, for example, Raven, 1945), but the known toxicity of these substances to tissue cells makes their field of utility somewhat questionable on the basis of the desiderata of burns treatment set out earlier in this paper.

As for the alleged "accelerators" of healing, their use still rests on insecure foundations, and their value, if it exists, is likely to be confined to the small burn which will, in any event, heal quickly if protected from infection and added trauma. The methods used at Glasgow have the great merit of simplicity, and of having been critically tested in large series of patients with a high degree of success, and the same applies to the "pressure dressings" treatment which is now so widely practised by American and Canadian surgeons. Both procedures have been found effective in preparing extensive burns for skin-grafting with the minimum of delay, which is one of the essential requirements of a treatment for burns. The best cover for a cutaneous burn is the patient's own skin, and the object should be to restore that cover as soon as possible.

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* [Papers by Dr D. P. Cuthbertson in this (BMB 691) and an earlier (BMB 486) number are of interest in this connection.—Ed.]

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THE PHYSIOLOGY OF CONVALESCENCE AFTER INJURY

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Convalescence is the recovery of health and strength after illness. The act of applying external measures to accelerate the return of the patient to normal, particularly by physiotherapy, occupational therapy and other psychosomatic means, has been termed rehabilitation. Rehabilitation measures should extend from the time a disability is sustained to the point when the individual resumes a normal existence, or the nearest to it that any irreversible change will permit. The process may involve not only problems of medicine, surgery and the ancillary specialties, but psychological, sociological and industrial problems of considerable moment to the individual, if not also to the nation. To obtain the best results it is necessary not only to have expert medical treatment, but also to have the patient's welfare reviewed and his treatments co-ordinated by a doctor of broad and deep understanding. This width of outlook is becoming of increasing importance in view of the tendency to specialism.

That our North-American colleagues are sharing in this deepening consciousness of the problem is demonstrated by the recent Symposium on Physiological Aspects of Convalescence and Rehabilitation held under the auspices of the American Physiological Society (1944). Although war has induced us to review intensively the whole system of convalescence and rehabilitation, in order to secure the return of the maximum number of men to the fighting line in the minimum time, this impetus for research should be carried on in peace-time.

For convenience the main problems of convalescence and rehabilitation can be divided into those which are primarily physical and those which are largely psychological. Psychosomatic relationships exist between these two groups. These will be discussed in relation to recovery from injury.

The physical problems can be divided into two groups: (1) those concerned with studying the nature, prevention and restitution of tissue-loss (by protein-loss and post-traumatic anaemia), and (2) those concerned with the more purely local problems of the cause and prevention of delayed union in fractures, and of preservation or restitution of joint-mobility and muscle-power.

Psychological influences play a large part in convalescence, which is only too liable to be a period of introspection with resulting enfeeblement of purpose. From the psychological aspect the essential aim is to recreate the patient's will for work and service.

Protein Depletion: General Considerations

Protein depletion following moderate to severe injury is essentially due to one or more of five main causes: (i) actual loss of tissue, (ii) loss of blood or exudate from the traumatized area, (iii) loss due to excessive protein catabolism and to the general reaction to infection, and (iv) loss due to disuse or reflex-atrophy. If, for example, a rough assessment is made of the protein losses over the first ten days or so, in a case with a burn involving the whole thickness of skin and 60% of its surface, the following quantitative data may be obtained (Cuthbertson, 1945):

- 1 Protein in the mass of skin and other underlying tissues destroyed, together with the leucocytic response involved in the separation of the sloughs 700 g
- 2 Protein lost in the exudate from the "weeping" surface, especially of superficial burns, but present also during sloughing and the granulation period, when the exudation may be copious 600 g
- 3 Excessive nitrogen excretion (mainly as urea) due to the catabolic reaction to trauma, which also involves considerable urinary losses of sulphur as inorganic sulphate and phosphorus as phosphate and leads to a loss equivalent to some 700 to 800 g protein. This reaction to trauma is accompanied by slight fever ("traumatic fever"). It is impossible to give a value for the protein-loss consequent on the coccal infections of the first week, and the abundant mixed coccal and bacillary

infections of the second to fourth week when the necrotic tissues are separating. The continued fever and chronic suppuration lead to a continued loss of tissue-protein.

- 4 Protein-loss resulting from atrophy—due to disuse and to reflex action may possibly be in the neighbourhood of 100 g
- 5 Skin-grafting operations, although probably not inducing further catabolic loss of protein, nevertheless contribute in some measure to the state of depletion. Quantitative data on this are, however, lacking.

In injuries such as fractures, dislocations, and even meniscectomies, the protein-loss is due to two factors: atrophy, and excessive catabolism of body-protein (Cuthbertson, 1929, 1932a, 1936, Howard, Winternitz, Parson, Bigham, Eisenberg, Stein & Reidt, 1944). Of these two factors the excessive catabolism of protein, which reaches a maximum usually between the fourth and eighth day in injuries due to direct violence, constitutes the major cause of protein depletion. Its nature has recently been reviewed (Cuthbertson, 1942, 1944, Peters, 1944, Armstrong, 1944).

The available evidence indicates that the excessive amounts of nitrogen, sulphur and phosphorus which appear in the urine are derived from protein, and the S/N ratio suggests, but does not prove, that muscle protein may be its source. In addition, there is a loss of creatine. The negative nitrogen balance in the first 10 days following a fracture of the leg may amount to as much as 137 g nitrogen, equivalent to some 856 g protein, or 8% of the total body-protein. This is some 3 to 4 times the total protein-content of the liver. Disuse-atrophy, though a contributory factor, does not form an adequate explanation (Cuthbertson, 1929, 1942, Howard *et al.*, 1944). The increased catabolic processes are more general than local, and appear to be conditioned by a mechanism which leads to (a) a raiding of the body-protein in order to supply endogenously the necessary substrate of amino-acids for the reparative process, and perhaps (b) a mobilization of oxidizable material for the enhanced metabolism of the healing process and for the "alarm reaction" of Selye (1940). It has been suggested that this mechanism exists for the purpose of permitting the healing process to be independent of food supply (Cuthbertson, 1932a). The so-called "toxic destruction of protein" in fever may also be explained in this teleological fashion. Cuthbertson (1930, 1932a) and Howard *et al.* (1944) have demonstrated that orthopaedic operations result in smaller negative nitrogen-balance than that after accidental injury.

When an animal has been depleted of its protein reserves, no increase in the loss of body-protein occurs on fracture (Munro & Cuthbertson, 1943), and more recently Munro (personal communication) has found that, in animals with fractures, the greater the proportion of protein in the diet before and after injury, the greater the nitrogen loss. Peters (1944) and Howard *et al.* (1944) have pointed out that in the malnourished subject injury produces little or no rise in nitrogen excretion. The writer and his colleagues have found that both the protein and the energy-content of the diet play some part in diminishing this loss of protein in fracture cases (Cuthbertson, 1936, Cuthbertson, McGirr & Robertson, 1939), but even diets of high calorie-value (up to 5000 Cal), and of very high protein-content, still fail to prevent a negative nitrogen-balance at the height of the catabolism—a finding comparable to that noted by Coleman & Du Bois (1915) and by Lauter & Jenke (1925) in typhoid fever at the height of the infective process. Howard *et al.* (1944) have also confirmed that the negative nitrogen-balances at the height of the catabolic process are still negative even when the calories and protein of the diet are raised to a considerable extent.

The observations of Taylor *et al.* (1943a, 1943b), Browne, Schenker & Stevenson (1944), Hirshfeld *et al.* (1944a, 1944b) and Co Tui, Mulholland, Barcham & Breed (1944) seem to

show that it is possible to diminish this nitrogen-loss in burns by giving a diet of high carbohydrate- and protein-content. The experimental work of Croft & Peters (1945) demonstrates that in burned rats the negative nitrogen-balance can in a large measure be suppressed by doubling the protein intake in the diet and also by the inclusion of 1% *dl*-methionine in the diet. This very important observation fits in with the conception of a raiding of whole protein molecules for one key amino-acid. It is very essential that this effect of methionine should be examined in man, for the protein loss is probably relatively greater in man than it is in the rat, in which there is little loss by exudation.

Following this catabolic phase where protein-depletion is the most marked feature, the patient frequently enters into a period when, through lack of appetite, the loss of protein is not rapidly made good. Howard *et al* (1944) noted that the negative phase, on average hospital diets, extended over an average period of 36 days. From the fourth to eighth day onwards, following moderate and serious injuries, or rather earlier after operation, active steps should be taken to replace that which is lost by dietary means. Transfusions of blood, plasma or serum should already have been instituted to make good their loss if this has been serious. In previously-depleted subjects this phase of excessive catabolism of protein does not apparently take place, and active steps may be instituted at an earlier date (Howard, 1945). Before going on to study the quality and quantity of the diet, a brief account will be given of another feature which is related to protein depletion and which accompanies moderate and severe injury, namely, post-traumatic anaemia.

Post-traumatic Anaemia and Depletion of Plasma-protein

The anaemia which develops after all serious forms of trauma, has recently been the subject of much intensive study. Grant (1944) has found that a haemorrhage of 20% of the total blood-volume (about a litre in the average man) may be expected to reduce the haemoglobin level from 100% to about 85% when the compensatory increase of plasma is complete or nearly so (usually within 48 hours after wounding). Losses of about 40% and 60% of the blood-volume may be expected to reduce haemoglobin to about 70% and 50% respectively. The actual fall is often greater. Blood volume studies show that, after injury, and although bleeding is arrested and obvious infection remains in abeyance, the erythrocyte volume continues to decrease for several days at a rate that varies in different cases. The meaning of this is not yet understood, but it is essential to take all possible steps to maintain the haemoglobin at least between 60% and 70%. It is still unknown to what level the haemoglobin may fall without interfering with recovery from potentially infected wounds.

Following on the initial period of haemoconcentration in severe burns, there is a reduction in the erythrocyte levels, a feature common to burns of almost all degrees, and Brown (1944) considers that this anaemia is haemolytic in origin, damage to a portion of the erythrocytes occurring at the time of burning. The anaemia tends to worsen in severe burns, reaching a maximum in 10-14 days. How far it is due to sepsis, and how far to depletion of body-protein through injury, is not easy to determine. Brown believes that failure of erythrocyte production cannot explain the rapid development of a reticulocyte response which occurs in those who recover, and it would appear that at this stage marrow dysfunction is not a significant factor. But in the later stages, with failure to recover after one or more months and without evidence of progressive blood destruction, defective marrow-function may well be responsible for the chronic anaemia which persists until the body temperature has settled and the healing is well advanced. This anaemia corresponds in many of its features with that seen in other chronic infections (Vaughan & Safi, 1939). Although Ryland (1942) has produced some evidence that depletion of body-protein may be a contributory factor, it is not conclusive. Sepsis and the requirements for the repair of large areas of denuded tissue are the factors apparently responsible for the anaemia. When sepsis can be eliminated the drain on body-protein is reduced, healing is accelerated, and anaemia usually diminishes. The wasting or cachexia of the body consequent on wound sepsis has been termed by Rusakov (1943) "wound phthisis". How far there is an actual inhibition of haemopoiesis in response to a toxin, or how far the haemopoietic system suffers in competition

with the area of healing for available protein, is obviously very important to determine. The observations of Schoenheimer, Rattner, Rittenberg & Heidelberger (1942) indicate that both the protein and the porphyrin of the haemoglobin have a lower "chemical activity" than the plasma proteins.

In famine-oedema resulting from protein deficiency, it is really only the albumin fraction of the plasma which seriously suffers depletion (Bruckman, D'Esopo & Peters, 1930, Bruckman & Peters, 1930, Peters & Eisenman, 1933, Weech, Wollstein & Goeltsch, 1937), and in the absence of haemoconcentration, reduction of this moiety is recognized as a diagnostic sign of protein deficiency. Weech *et al* (1937) have pointed out that, because the variation of albumin in normal plasma is so great, and because the plasma volume tends to contract as the concentration of albumin falls, there must be considerable depletion of protein before hypoalbuminaemia becomes conspicuous. In view of this, the reduction in the plasma proteins (which is essentially a reduction of the albumin fraction) found in severe burns and other serious injuries is an indication of the degree of depletion of the protein reserves (Taylor *et al*, 1943a, Anderson & Semeonoff, 1944). If infection is present, the globulin may rise. Protein depletion appears also to affect both natural and acquired immunity reactions (Cannon, Wissler, Woolridge & Benditt, 1944).

Energy Requirements with Particular Relation to Protein Loss

The energy requirements of an uninjured healthy person lying in bed are probably in the neighbourhood of 2,100 Cal. The energy expenditure will rise as the result of an injury, an infective process, or a condition which causes restlessness. For example, the writer found a 40% rise in the basal oxygen-consumption of an otherwise normal subject between the 6th and 7th days following the fracture of a tibia by direct violence (Cuthbertson, 1932a). This period of enhanced energy-expenditure, which was paralleled by a rise in body-temperature, was found to subside in some 10 to 12 days. During the post-catabolic phase, although well-defined anabolic processes are taking place in the healing zone, yet atrophy may result elsewhere through immobilization. What are the increments in energy requirement for the reparative process? Growth in the adolescent is accompanied by the laying down of tissue equivalent to a value of 50 to 80 Cal daily (Terroine, 1936, Mitchell, 1944), in pregnancy, the formation of foetal tissue is equivalent to a daily storage of some 25 Cal (Mitchell, 1944), in lactation, the calorie-equivalent of the protein, fat and lactose present in the milk, which may amount to 1,000 ml per day, is 660 Cal. Even to replace the protein and fat lost in the course of the illness following a burn involving as much as 60% of the skin (total thickness), a patient might conceivably deposit some 500 Cal daily in the shape of new protein and lipid. It is thus improbable that the calorie requirement for a person convalescing in bed would exceed 3,500 Cal.

Mitchell (1944) has pointed out that normally the satisfaction of the body's requirement is left entirely to the appetite, and in the healthy person the appetite adjusts to a remarkable degree the intake of food-energy to the requirement. The human appetite, however, cannot be relied upon to adjust the intake to the correct requirement of the essential nutrients. There is no doubt that, in general, the demand for calories is paramount, and that within certain limits the body does not exhibit signs of specific deficiencies of individual nutrients until these have existed for some considerable time. The work of Amantea (1924) and Westerbrink (1934) point a warning to the long term effects of attempting to cover the caloric requirement of the diet if it is ill-balanced, for the greater the intake of a deficient diet, the quicker does the deficiency appear to develop.

Even normal subjects, on a normal diet, can be made to store nitrogen and sulphur if they ingest food of greater energy value than their energy expenditure and anabolic processes normally require. The writer and his colleagues (Cuthbertson, McCutcheon & Munro, 1937, Cuthbertson & Munro, 1937) found that it was possible, by giving some 25% more calories than were required for maintenance, to induce a reduction in the urinary nitrogen and sulphur excretions of some 3.72 g and 0.287 g, respectively per day, and this was accompanied by an increment in body-weight. Carbohydrate was superior to fat in this respect. When excess food is given, the body appears to burn what it can

and store what it cannot burn. The capacity for storing carbohydrate being strictly limited, storage of protein and fat takes place. This laying down of protein in the normal uninjured subject appears to be but temporary, and on resumption of a normal level of energy intake, the stored nitrogen tends to be excreted. In the anabolic phase of convalescence, additional storage of protein may take place if the patient can be persuaded to take food of a caloric value in excess of requirement, for again the organism, confronted with more food than it needs, stores both what it immediately requires and what it cannot burn.

It is not known whether this storage-effect fills the void caused by the injury more quickly, or whether the protein is again laid down in some but temporary store which is readily catabolised when the intake of energy-yielding foods returns to actual requirement. On the whole this would seem unlikely, but further investigation is necessary. Such a diminution in the extent of the nitrogen loss as has been noted to occur in injured patients receiving high-calorie diets may be due to the protein-saving effect of the excess food—affecting a phase of protein metabolism which is not that concerned in the catabolic response, but which nevertheless masks the latter when the nitrogen metabolism is assessed from input and output data.

Dietary Protein

Protein generally supplies some 10% to 12% of the total calories of the diet of adults in Britain at all levels of energy expenditure (Cuthbertson, 1940). Even in the growing infant subsisting on its mother's milk, protein forms only some 8% of the calories, and this at a period when the total energy requirements in relation to the anabolic requirements are low. When a variety of natural foodstuffs is used, the body's normal requirements for the essential amino-acids or specific groupings will almost certainly be covered, and the distinction between first- and second-class protein tends to disappear. When the body is injured and the process of healing is taking place, it is, for example, natural to conjecture that the requirement for the repair of injured muscle will best be met by the ingestion of muscle. Although it is conceivable that this may be so, the evidence suggests that the organism is not thus dependent on the quality and quantity of the ingested amino-acids, but that through processes like those of deamination and reamination it can fashion from endogenous or exogenous sources the appropriate substrate for the synthetic processes.

If attempts are made to establish nitrogen equilibrium in injured cases, during this early catabolic period when the organism would appear to have geared the non-injured parts to an anti-anabolic phase, it is found that, with rise in dietary protein-intake, more nitrogen appears in the urine of the patients concerned. It is highly probable that, in a previously well-nourished subject, the dictates of appetite will, in general, condition the optimal amount of food that is needed during this period, particularly in terms of energy requirement, and that there is no real indication to attempt force-feeding, indeed this might even cause harm. Howard *et al* (1944) found that otherwise healthy patients "cannot, or will not, eat more than limited amounts during the early periods of convalescence."

When this catabolic phase is diminishing around the 5th to 9th day, the patient should be encouraged to eat as much as he conveniently can, particularly in the case of patients with burns, and as the requirement of protein for repair and recovery of depleted reserves may be very considerable, this should be present in the diet in sufficient amounts to meet his needs during the recovery period, and nothing should be lacking in the diet which will impede this object. In this connection it is essential that there shall be sufficient carbohydrate and fat to permit the maximum anabolism of tissue protein by covering the energy requirements.

In convalescence, a protein intake of about 150 g per day would appear to be indicated in, for example, the process of replacing ultimately the 2 kg of protein which may be lost during the first 10 days following a third-degree burn extending over 60% of the body surface and involving the whole thickness of skin. Fortunately not all injuries are of this magnitude.

Milk, particularly skim milk, cheese, eggs, reconstituted dehydrated ground meat or ordinary cooked meat, and fish will form the basis of the supply of animal protein, cereals that of vegetable protein.

In facio-maxillary injuries and other conditions where the administration of normal forms of food by mouth is precluded, it is most convenient to give the diet in the form of a "mush" by tube. New developments, in the shape of dehydrated high-protein high-calorie food blocks, form a suitable basis for preparing this "mush." Ground meat with its extractives is appetising. Ordinary milk reinforced with dried skim milk, egg flips, cereal preparations, cream, etc., have long been used as a means of obtaining adequate protein and calories. It is always necessary to review such diets to ensure that there is no prolonged deficiency of any vitamin or mineral.

It should be noted that, if it is required to increase the intake of protein and the level of energy requirement is already covered, this can most conveniently be done by reducing the amount of fat in the diet, as rather more than twice as much protein can be added as there is fat subtracted. Similarly, if it is desired to increase the total intake of food and the satiety value is being approached, non-fatty protein-containing foods, such as skim milk, can usually be added to the diet in the form of in-between-meal feeds, particularly if suitably flavoured and made up as milk shakes. Where operations have to be performed on depleted patients, steps should be taken to replenish the tissues before operation.

As it is not only unnatural but often distressing, and at any rate unpleasant, to be fed by tube or parenterally, any departure from the normal route should be undertaken only if the patient's condition demands it. Where there is any condition which is likely to impair seriously the ingestion, digestion or absorption of food over a period of time, then protein may be given in a predigested form, together with sufficient glucose.

Anorexia

Many factors inhibit gastric tone and motility, and patients convalescing from injury or disease often suffer from loss of appetite during the early phase of recovery. In order to prevent deterioration through further protein-depletion, it is essential to encourage the patient to eat as much as possible without at the same time causing any untoward reactions such as nausea, vomiting and abdominal distension. Food offered is often not eaten owing to pain or to delayed gastric evacuation, and the quantity of the residue is often surprising. The sense of thirst should as far as possible not be dulled by consuming large volumes of water or other non-nutrient fluids, and whenever practicable all fluids drunk should have a nutrient value. Physical exercises may also stimulate appetite by increasing gastric tone and motility. In general, the patient should receive at least 5 g sodium chloride daily unless there is oedema. The intelligent use of salt may increase the desire for fluid.

It may be that loss of gastric tone is not the sole cause of anorexia, but that there is a disturbance of the appetite-mechanism. Quigley & Solomon (1930) have reported that one of the best means of improving gastric tone and motility, provided there is no vitamin-B₁ deficiency, is the administration of insulin. Higgins & Ostlund (1934), Bram (1940) and Polotner (1932, 1938) have also found insulin of value. Ivy & Grossman (1944) have suggested that 10 to 20 units 1 hour before a meal may prove of value to the convalescent. Insulin, however, should be used only when there are clear indications that something must be done to prevent a decline in the patient's condition, and should not be continued unless there is an increase in appetite as the result of this treatment. Ivy & Grossman (1944) have concluded that defective secretion of digestive juices is not a problem in convalescence, motor dysfunction being more likely to be the origin of anorexia and constipation.

Protein Hydrolysates

Parenteral feeding must always be regarded as a temporary substitute for normal eating, and should be confined to conditions where the ability to ingest, digest or absorb protein is seriously impaired. Total alimentation with an enzymic hydrolysate of casein and glucose over a period of 40 days has been recorded by Albright (1944).

The use of protein hydrolysates has recently been reviewed by Elman (1943), Martin & Thompson (1943), Gaunt (1944), Peters (1944) and Cuthbertson (1944). A properly-prepared enzymic or acid hydrolysate of casein can be obtained and this material can be injected intravenously, usually without inducing pyrogenic or other untoward reactions. Obviously

a safe product has distinct uses in conditions where, through injury or disease, the patient is unable to ingest or absorb from the intestine sufficient amino-acids to meet his requirements. An acid hydrolysate requires to be reinforced with tryptophane to make good the loss during hydrolysis. Insufficient is as yet known about the nutritive qualities of acid hydrolysates. These will require careful comparison with the enzymic hydrolysates in the light of the recent observations of Madden, Woods, Shull & Whipple (1944) that an acid hydrolysate reinforced with tryptophane was apparently inferior nutritionally to the enzymic product.

Casein hydrolysates are usually prepared in 5% concentration dissolved in 5% glucose solution, or a 5% solution is given simultaneously with 5-10% glucose solution, the latter being administered at the same rate or at twice the rate of the hydrolysate. This last method involves the introduction of very large volumes of fluid and may lead to oedema in those with low plasma proteins. Local thrombosis sometimes results, particularly during long infusions with higher concentrations. Care should be taken to see that the needle extends well within the vein beyond the insertion of a tributary, and that it does not occlude the lumen. One and a half litres per day of a 5% solution is required to meet the normal basic requirement of 1 g per kg. As the amount of protein available for anabolic purposes is conditioned by the caloric value of the diet, the energy requirement should be covered.

It has been customary with enzymic and acid preparations to recommend neutralization to a pH of 6.5 with NaOH before use. When this is done, a concentration of 0.3% NaCl usually results (National Research Council, 1944).

The rate of administration of glucose should not exceed 0.85 g. per kg. per hour, which represents roughly 10 ml per minute. The rate of infusion of a 5% hydrolysate should probably not exceed 3 ml per minute. There is a liability to the development of oedema with the administration of large quantities of solution, not only in the case of those who are on the verge of nutritional oedema, from undernutrition, but also in those with traumatic anuria or oliguria.

The components of the B-complex appear to be associated with the optimal utilization of carbohydrate. During short and moderate periods of illness it is probably not necessary to consider supplementation of such hydrolysates with vitamins. If required, aneurin (thiamin) (2 mg.), riboflavin (2 mg.), nicotinic acid (20 mg.) and ascorbic acid (50 mg.) can be given daily if this mode of therapy has to be used over a period of time or there has been deprivation beforehand.

Pure Amino-acids

Shohl & Blackfan (1940), Madden, Carter, Kattus, Miller & Whipple (1943) and Bassett, Woods, Shull & Madden (1944) have demonstrated that mixtures of pure amino-acids are suitable for injection in conditions where the parenteral administration is necessary for protein nutrition. Preliminary accounts would indicate that they can be given in higher concentration and with greater rapidity without causing untoward reactions. These pure amino-acids are at present so costly as to make it possible to do only a very few clinical experiments at a time.

Casein digests may be given orally or by gavage. Unfortunately they are rather unpalatable. Hydrolysates of meat are distinctly better. It is very necessary to emphasize that the use of hydrolysates and pure amino-acid mixtures is still in the stage of clinical trial and it may well be found that present enthusiasms for their wide use will subside and their proper role in illness be determined.

Blood, Plasma and Serum

Peters (1944) has stated that neither blood nor plasma appears to be an efficient source of protein for general nutritive purposes, compared with hydrolysates of high-class protein, although they specifically correct anaemias and plasma protein deficits. Further investigation is, however, necessary, particularly in view of the statement by Fink, Euns, Kimball, Silberstein, Bale, Madden & Whipple (1944), that all the nitrogen requirements of the dog can be supplied by dog plasma by vein.

Disuse- and Reflex Atrophy

It has long been observed that the muscular wasting associated with bone or joint diseases is more rapid and

extensive than that which occurs with simple disuse. In the former, an apparent loss of substance may be seen in a day or two, and in acute cases the wasting is very definite in 1-2 weeks. It is quite definite also that there is a more rapid and extreme wasting in limbs immobilized for some inflammatory or traumatic lesion, than in limbs immobilized to correct a deformity. The extensors are the group of muscles chiefly affected. The history of the differentiation of these two types of wasting has been a source of speculation since the days of Hippocrates.

There would appear to be two quite distinct types of atrophy: one which is mainly of reflex origin, and one which is probably entirely due to imposed rest. The latter is generally superimposed on the former. Treatment of the former will be conditioned by the rapidity and effectiveness of the healing process in the case of trauma, and of the subsidence of the inflammatory process in arthritic conditions. Movement of the affected parts, so long as they do not adversely affect the healing zone or the inflammatory process, are probably of advantage, in that they will tend to counter the superimposed atrophy of disuse.

It is well known that, in addition to an atrophy of muscle, there may also be an atrophy of connective tissue, exemplified by the osteoporosis seen in inflammatory conditions affecting joints, etc., and also in pure disuse (Allison & Brooks, 1921, 1922).

To determine the effects of pure disuse, the writer (Cuthbertson, 1929) subjected normal adult volunteers to periods of inactivity produced by immobilization of a lower limb in a splint. It was found that these subjects, previously in nitrogen-equilibrium, exhibited within 2-3 days an increased urinary excretion of nitrogen, sulphur, phosphorus and, in less degree, calcium. There was in addition an increase of the amount of calcium and phosphorus in the faeces as the period of rest lengthened. A small but apparently definite reduction in heat-production took place during the period of imposed rest.

A reduction was noted in the volume both of the immobilized leg and of the other leg held more loosely at rest between sandbags. This reduction is probably largely conditioned by the degree of reduction of the capillary bed in the resting muscles. It is realized that such experimental conditions cannot reproduce the degree of immobilization which a severe injury dictates.

Rest in Bed

Although orthopaedic surgeons have for years been gradually reducing the period of bed rest for their patients, it is only within the past year or two that the whole problem of rest as a therapeutic agent has come up for revision. Recently a series of articles on the abuse of rest has appeared in the *Journal of the American Medical Association* (Harrison, 1944, Eastman, 1944, Powers, 1944, Dock, 1944, Ghormley, 1944, Menninger, 1944). It has long been considered that prolonged rest in bed and severance from work are absolutely necessary in the management of the more serious forms of heart disease. However, Harrison (1944) reviewing the situation, has found no proof that rest in bed carried out many weeks after symptoms have disappeared is of value in cases of congestive heart failure, angina pectoris or myocardial infarction, and that from the psychological standpoint there is a definite disadvantage in the enforcement of a rigid regimen after the acute stage. In two cardiac conditions, namely myocardial infarction and acute rheumatic carditis, it is probably safer to err in the direction of a too-long period of rest.

In the otherwise healthy subject, the healing of wounds of different structures is fairly uniform for the structure concerned, and requires a definite time. To secure this it is obviously necessary to effect closure where possible and protection for the repair process. How far it is necessary to have complete bodily rest for the healing process is now in doubt for, rather contrary to expectation, those who have advocated early post-operative movement have apparently observed no deleterious effect, no increase in pain, no greater frequency of disruption or hernia (Powers, 1944). Caution is certainly needed in assessing enthusiastic reports but it does appear that we have here a problem that requires careful study, in particular of the materials used in suture. In the writer's view, any quickening of metabolism, provided the injured area shares in the increased blood flow, should improve the healing process and prevent wasting through disuse (Barclay).

Cuthbertson & Isaacs, 1944) What would be deleterious to the healing process would be a level or form of activity which diminished the blood flow and the supply of substrate to the healing zone. If increased activity leads to a more than proportionate increase in the dietary intake this is of great importance, if it does not, then it should be temporarily abandoned. Ambulation should be deferred in patients showing considerable debility.

Bone-atrophy, muscle-wasting and vasomotor instability are associated with prolonged rest in bed so also is thrombosis of the deep veins of the pelvis and leg. Early movement in bed is of particular importance in pelvic and abdominal operations, and there is no doubt that the psychological effects of early walking are very considerable, and convalescence is denuded of many of its complications.

The Causes and Prevention of Delayed Union of Fractures

With the conviction that the surgeon cannot be reminded too often of the factors which may play a part in delaying union of a fracture, a Sub-committee of the Medical Research Council War Wounds Committee has recently drawn up a memorandum (Medical Research Council, 1944) which emphasizes that a clear distinction must always be drawn between delayed union and established non-union. In the former condition, union is possible and will eventually take place if the immobilization is maintained for a sufficiently long time, in the latter, operative measures are necessary before union is possible. Non-union is comparatively rare, and is generally avoided by reasonable apposition of fragments, delayed union is frequent, and is due to one or more of the following causes, the first three of which are obviously beyond the control of the surgeon

- a gross comminution or double fracture
- b deficient blood supply
- c inherent inability to form callus¹
- d insufficient apposition
- e inadequate and/or interrupted immobilization, late setting or resetting, particularly during the 3rd and subsequent weeks
- f too early abandonment of complete immobilization
- g distraction or overpulling during treatment
- h retention of transfixation-pins for too long a period
- i weight-bearing in the presence of mal-alignment
- j infection in compound fractures, particularly when comminuted. Some degree of infection is often inevitable, but its severity and extent are largely controllable by early and adequate surgical treatment combined with penicillin or other effective agents
- k severe and inadequately-treated injury of the soft tissues, particularly the muscles in open wounds
- l local delaying effects of certain bacteriostatic or bacteriocidal drugs when present in excess

As the organic basis of the calcification process is protein, it may be affected by disturbances in protein-metabolism and share in any serious depletion of protein. Thus Rhoads & Kasinkas (1942) were able to produce a definite retardation in the formation of the bony callus in defects in the ulnae by lowering the plasma-protein level of dogs to approximately 4.0 g per 100 ml by repeated plasmapheresis.

Bone-plating

Space does not permit discussion of the indications for and against bone-plating as a means of assisting the union of long-bone fractures, nor has the present writer the necessary experience in this field.

Tests of Physical Fitness

As present developments in rehabilitation therapy are primarily designed to return the patient to his work in as good a condition as is possible and in the shortest time, or to train him for some new occupation, attempts have been made to devise tests of fitness. No single test can obviously measure that rather indefinable condition which comprises an infinite variety of closely interrelated functions, and it is not surprising that various kinds of psychomotor, mechanical, and exhaustive performance tests have been devised.

¹ [For a discussion of the relationship of vitamins and hormones to bone-healing, see the contribution in this number by Dr G. H. Bell (*BMB* 686) —Ed.]

According to Keys (1944) the measurement of the maximal oxygen transport appears to be a good test for combined respiratory and cardiovascular fitness. Tachycardia in response to exercise or tilt-table is of some value. Just how far these tests are useful is at present questionable. Wise clinical judgment, though not quantitative, is probably safest. The function of the heart is of importance even in persons convalescing from diseases which do not primarily affect it, for it may become secondarily affected. The heart, too, is the focal point in effort syndrome, even although there is no evidence that there is a primary disorder in the heart.

Physical exercise tests are also a test of peripheral circulatory adjustment, as well as of cardiac and respiratory function. Incompleteness of adjustment to normal conditions is usually manifested by faintness, "giddiness", dimness of vision, tachycardia, palpitation, deepened respiration and weakness. Normally the vasomotor system adjusts the vascular area to prevent cerebral anaemia developing. The disappearance of the circulatory maladjustments which accompany illness is a gradual process.

Wollheim & Lange (1931) have drawn attention to the slightly decreased circulation-time in fever, and this has also been noted by Bellis, Doss & Croft (1943) after operations. The present writer has drawn attention to the initial period of depressed bodily function that immediately follows a moderate or severe injury, and which is coupled with a depression of heat-production, body-temperature and oxygen consumption (Cuthbertson, 1942). Mann (1918) noted that after pneumonia the ability of convalescent patients to adjust to exercise, as measured by their blood-pressures after graded work, took some 8–17 days to return to normal. He found that the blood-pressure was a more sensitive index of progressing convalescence than was the pulse-rate. Much more work in this direction is obviously needed.

The proper functioning of the peripheral circulation involves more than the proper and normal functioning of their nerve supply and reflexes, for the venous return from the periphery is conditioned by the intra-abdominal and intra-thoracic pressures, which in man may be governed by the tone of the muscles. Henderson, Oughterson, Greenberg & Searle (1935–36) have demonstrated that the pressure inside the biceps of patients in bed is lower than that of healthy controls. Kerr & Scott (1936) have also examined this, but have found it of no prognostic significance. Early supervised exercises in bed, followed by other physical reconditioning systems, have proved their value. Above all it is necessary to quicken the spirit of the convalescent so that he is keen to extend his activities. Routine is boring, and every day should lead to some measure of fresh activity.

Physiotherapy and Occupational Therapy

Some form of physical therapy is applicable to almost every type of injury, except possibly certain conditions which require complete rest. The various activities commonly employed at the different stages of a rehabilitation programme have been defined recently by the Ministry of Health (1943). In general, it may be said that such stages should be built on the following lines:

- a *Passive physiotherapy* heat, massage and electrotherapy should be used only for a minority of patients, chief reliance being placed on active movements. (The author found that even when massage supplemented with passive movement was applied to patients convalescing from fractures of the long bones, a decreased excretion of nitrogen, sulphur and phosphorus in the urine took place, indicating anabolic effects (Cuthbertson, 1932b).)
- b *Active movements* remedial exercises to restore function to the injured or diseased region, and to condition the body generally, should be begun in bed as early as possible. The impulsive movements of games and sports break down the protective safeguards which the patients are apt to erect round their injuries.
- c *Occupational and industrial therapy* this should be directed to placing the man back in his original occupation, or if he is not fitted for that, steps should at once be taken to determine what is the next best thing he can do and would like to do, and then to train him for it so that there is not a tiresome gap between leaving hospital and resettlement in work. Amongst others

McIndoe (1943) has reported excellent results on these lines. Some of the larger industrial works may find it advisable to develop rehabilitation workshops of their own.

d. *Lectures, debates, etc.* these are useful during the period of physical relaxation, and they quicken the man's intellectual processes and prevent him brooding.

e. *Social care* it is very necessary that the patient's convalescence shall not be impeded by personal or domestic anxieties. The organization of social security will do much to avoid this, and it is here that the hospital almoner will find her most useful sphere of work.

The value of rehabilitation measures can be appreciated from Watson-Jones' statement. (1942) that some 85% of injured men in the R.A.F. are returned to full duty.

Some of the primary problems which require investigation have been defined by Balme (1943). There are many others. Such questions include: when and to what degree movement is beneficial after trauma of the soft tissues, the relationship of pain to immobility, and the conditions under which pain should be abolished and movement promoted, the precise place of movement in the treatment of fractures, the factors influencing the full return of function to joints after operative procedures, the relation of trauma and arthritis, the burnt hand, the relative value of movements which are part of an exercise and movements which are essentially purposeful or impulsive.

Psychological Problems

Space does not permit of discussion of the many problems of post-traumatic personality-changes, apart from noting

that the disfigured patient and the long-term case present psychological difficulties which can in some considerable measure be overcome, not only by functional re-education, but by continuously reminding the patient of what he will be like and what he will be able to do when finally rehabilitated.

Conclusions

In this brief account of convalescence it has been possible only to touch on a few of its pressing problems. Most consideration has been given to the problem of protein depletion, particularly in burns, for this has been largely neglected in the past. Practically all clinical observations go to indicate that it is doubtful whether, during the early catabolic phase, any dietary measure can effectively suppress the catabolic destruction of protein. The recent observation that *dl*-methionine can in large measure do this in the burned rat is a notable contribution, and now awaits clinical confirmation. The administration of a large excess of protein (more than 100–150 g.) for the first few days after injury is not at present indicated, but advantage should be taken of the heightened synthetic process in the subsequent reconstructive stage to ensure that nothing is lacking in the diet which will ensure optimal convalescence, and every aid which surgery and the ancillary sciences can bring to this process should be sought. Active rehabilitation measures should be instituted from the first, for as John Hunter (1794) has stated, "There is a circumstance attending accidental injury which does not belong to disease—namely, that the injury done has in all cases a tendency to produce both the disposition and the means of cure."

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BIOCHEMICAL FACTORS IN THE AETIOLOGY OF "SHOCK"

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The initiating mechanism of the delayed systemic reactions following severe tissue injury is still a debated point. As it is still undecided whether shock is due to oligæmia conditioned entirely by local fluid-loss, to toxic factors (i.e. normal or abnormal metabolites set free in the injured area) or to a reflex nervous mechanism, a clear indication of a biochemical approach has not yet developed. Obviously, local loss of blood and/or plasma must play an important part even if we believe, as Moon, Morgan, Lieber & McGrew (1941) still do, that haemorrhagic shock and traumatic shock are distinct entities. The protagonists of the various theories have often not been disposed to recognize a combination of initiating factors, though such a tendency is now more apparent.

First Principles

Shock is as fundamental a reaction as inflammation, and we know little of the specific chemical factors involved in either, but it would seem likely that the two processes are in some degree linked. It is unlikely that two completely distinct mechanisms of dealing with the local and general effects of injury have evolved. In fact, histamine has been assigned an important role in both reactions. Obviously the profound bodily changes in shock must be accompanied by widespread biochemical changes in the tissues. For instance, the great reduction in oxygen-consumption probably accounts for many of the biochemical changes described, e.g. acidosis, loss of liver glycogen.

We are concerned here not with effects but causes. Are some or all of the reactions of traumatic shock primarily induced by a chemical factor(s) released at the site of injury? As the oligæmia of shock must be in some degree a result of rapid local plasma-loss, all the reactions cannot be thus explained even in the absence of haemorrhage, unless we assume that the same chemical factor(s) excite the local fluid-loss itself. If, however, local fluid-loss is the whole story, the search for chemical factors is an obvious waste of time. It is important then, to see what evidence there is against this widely supported hypothesis. There is no space for a complete review of this or any aspect of shock dealt with here. The review of Harkins (1941) covers the 1930-40 period and the books of Cannon (1923), Moon (1938) and Scudder (1939) should be consulted for earlier work.

There is recent evidence (Green, Dworkin, Antos & Bergeron, 1944, Best & Solandt, 1941) that, in shock following hind-limb ischaemia, the fluid-loss *per se* is not sufficient to account for death. Haist & Hamilton (1944) found that rats would recover after a usually lethal period of limb-ischaemia if the limb-clamps were re-applied at a time when local fluid-loss was practically maximal.

Is there any evidence that the blood or lymph draining from the injured area has a shock-inducing effect when transfused into a normal animal? The evidence is indeed conflicting, and none perhaps is conclusively positive, many have ruled the possibility out on the basis of negative results. Cross-circulation experiments have occasionally yielded positive results and recently Chess, Chess & Cole (1944) succeeded in killing dogs by the transfusion of blood obtained from the femoral vein draining a previously ischaemic limb. Kendrick, Essex & Helmholz (1940), in an elaborate per-

fusion experiment, found that repeated transfusions of blood from traumatized limbs produced a delayed fall of blood pressure and death a few hours later. Blalock (1943), a prominent protagonist of the local fluid-loss theory, found that thoracic-duct lymph from dogs in ischaemic shock produced shock in normal dogs, with a fatal issue in some. Following gross trauma to the limb, the results were not so impressive, but were considered suggestive. Katzenstein, Mylon & Winternitz (1943) confirmed this finding in animals shocked by the limb-tourniquet method.

The Search for Toxic Metabolites

Toxic metabolites as initiating factors in shock cannot therefore be dismissed outright and it is well to remember that, as a result of the work of Bayliss, Cannon, Dale and collaborators, the theory held first place after the last war. In the search for such substances many investigators have naturally confused initiating with incidental and terminal factors. The main approaches have been on the following lines:

i As a prominent feature of shock, at least in its later stages, is a fall in blood-pressure, all physiological vaso-depressor substances, as discovered, have been suggested as possible shock-inducing factors. Hence histamine and histamine-like substances early achieved prominence. Acetylcholine and choline compounds and, as we shall see in more detail later, adenyly compounds have all been suspected. Recently Westerfeld, Weisiger, Ferris & Hastings (1944) studied the shock-producing properties of callicrein, a vaso-depressor substance rich in some tissues. They describe its possible mode of action in traumatic shock.

ii Some of the blood constituents (e.g. K, P, HCO₃, lactic, pyruvic and amino-acids), whose concentration is increased in shock, have been suspected as possible culprits.

iii Endocrine dysfunction, particularly of the suprarenal glands, has been intimately related to the shock-picture.

iv As a great many tissue-extracts when injected intravenously have a depressor action, their effects have been linked with those of shock. The shock-like effects produced by intraperitoneal implantation of whole tissues has been much studied.

v A great variety of unrelated substances, such as peptone, bile, insulin, snake-venoms, and bacterial extracts, have been used as shock-inducing agents. The multiplicity of available methods points to the danger of suggesting that a shock-producing substance has any aetiological role in traumatic shock.

Histamine

Where have these methods of approach led? Of the depressor substances, histamine has led the field, and even at present it is not neglected (Hueper & Ichniowski, 1943). In spite, however, of many resemblances between the effects of histamine and traumatic shock, the importance of histamine in this connection has slowly declined. There are several reasons for this. There is no consistent evidence of an increase in blood-histamine in clinical shock (except possibly in burns), the rat, rabbit, and even the unanaesthetized cat, have a relatively high resistance to histamine, but

develop traumatic shock as easily as non-resistant species, extensive damage to muscle is a prominent precursor of traumatic shock, but muscle is a relatively poor source of histamine, even when a rise in blood-histamine has been found, the time relations or the quantities involved cast doubt on its aetiological significance. There is reasonable evidence that histamine appears in large amounts in the peritoneal transudate from a strangulated loop of intestine, but little evidence that it is responsible for the animal's death (Aird & Henderson, 1937, Maycock, 1938).

There is some evidence of an increase in the histamine of the blood following limb-ischæmia, though Kwiatkowski (1941) could not confirm this during reactive hyperaemia in man and the rabbit. The recent work of Anrep, Barsoum, Salama & Soudain (1944) may explain previous discordant results. They found in man that the increase in the histamine-content of the local venous blood can be detected only in the first minute after release of the obstruction. Thereafter, as reactive hyperaemia develops, the rapidly-increasing flow of blood dilutes the released histamine. If the venous pressure is raised so as to retard the venous return, the plasma histamine remains above normal for up to two minutes. The shock following prolonged ischæmia of the limbs is not essentially different from that following trauma. It would seem however, that, whilst histamine may be responsible in some degree for reactive hyperaemia and possibly for the immediate general symptoms (though Stoner & Green (1945a) could find no clinical evidence of this), it does not play any part in the later systemic effects which we term "shock." Peptone shock is probably due to histamine release (Holmes, Ojers & Dragstedt, 1941), though it is still debatable whether it plays the important role in anaphylactic shock previously allotted to it. Neither of these conditions is, however, intimately related to traumatic shock.

Of the other vasodepressants, only the adenylyl compounds have assumed any importance in relation to shock, they are discussed later.

Potassium

Of the blood-constituents altered in shock, potassium has received most attention because it is, in excess, a powerful poison to heart-muscle (Winkler, Hoff & Smith, 1939). Muscle is a rich source of potassium, much of which is lost following prolonged ischæmia (Bywaters, 1944). Scudder (1939) in particular has stressed its effective role in shock, but even his results suggest that its importance, if any, is only in the terminal phases of shock. Manery & Solandt (1941) demonstrated a rise in serum-potassium in traumatic shock in dogs, but found that only severely injured muscle loses any appreciable amount of potassium. Gutman, Olson, Knoll, Levinson & Necheles (1941) found a transient rise following severe trauma in dogs, and a small terminal rise. Rewell (1943) reports a rise following the release of limb-tourniquets in man. Winkler & Hoff (1943) have clarified the position in ischæmic shock by showing that, though there is a consistent rise in serum-potassium, the level reached is not usually sufficient to cause any cardiac embarrassment. It would seem then, that the rise in serum-potassium is a reflection of severe tissue-damage but is not an initiating factor in shock.

Hormones

The hormones (and now the vitamins) have naturally been linked with shock—which must ultimately affect every tissue and function in the body. The suprarenal glands have attracted most attention, and excess of the medullary and deficiency of the cortical hormones have both been suggested as exciting factors in shock. The occurrence of peripheral vasoconstriction and the rise in blood-sugar naturally suggested prolonged sympathetic stimulation, possibly due to an increased output of adrenalin. Such a concept was supported by the finding that prolonged perfusion of small amounts of adrenalin results in shock. In their latest paper, Freeman, Freedman & Miller (1941) describe this shock-inducing method, though they do not suggest that traumatic shock itself is due to the oversecretion of adrenalin. In fact, there is no clear evidence for this theory and, though recent work indicates the presence of a vasoconstrictor substance in the blood of shocked animals, its nature is not established. Dexter, Frank, Haynes &

Altschule (1943) and Hamilton & Collins (1942) present evidence that it is renin, though Page (1943) does not agree.

The role of cortical hormones has achieved much more prominence. Swingle and co-workers first pointed out the resemblance between the late effects of complete adrenalectomy and those of severe trauma. Adrenalectomized animals were found to be much more sensitive to injury. The more recent therapeutic trials with cortical hormones have been mainly negative or inconclusive (Noble & Collip, 1942, Helfrich, Cassels & Cole, 1942, Huizenga, Brofman & Wiggers, 1943), but Reiss, McLeod & Golla (1942) claimed some success, particularly with corticotrophin in dehydration-shock in rats.

The work of Selye (1937) showed that, after mild tissue-trauma, the adrenal cortex hypertrophies, and he suggested that the trauma-refractory state ("countershock") is due to increased cortical secretion. Tepperman, Engel & Long (1943) demonstrated cortical hypertrophy after many forms of injury, and suggested that the common responsible factor was a protein breakdown-product.

A possible link with this work is seen in observations on trauma-immunity. Noble (1943), Ungar (1943), and Green (1943) found that animals submitted to trauma are, after an interval, more tolerant to further trauma. Ungar claimed, moreover, that this resistance could be passively transferred to other animals by serum-injection. He has further shown (1944) that after trauma there is a substance in the serum which inhibits the release, *in vitro*, of histamine from blood, which is induced by peptone¹. This substance is produced by the pituitary gland and acts through the suprarenals and, of the preparations injected, corticotrophic hormone was by far the most active in raising its content in the animal's blood. It is noted that this finding does not directly link histamine with the effects of trauma, as the rate of release of other substances was not determined. To the writer it seems that it may be related to the claim that cortical extracts diminish capillary permeability (e.g. Menkin, 1940).

Although it is unlikely that a diminution in cortical hormone output is an initiating factor in shock, the role of the suprarenal cortex in modifying the degree of shock developed after trauma may yet prove to be important. One possible aspect of this is the relation of sodium depletion of the tissues to the outcome of shock. Complete adrenalectomy causes a severe fall in blood-sodium, a similar fall occurs in dehydration shock, e.g. acute intestinal obstruction. There is little precise information about sodium distribution in traumatic shock, but the work of Rosenthal (1943) may be relevant. He showed that the prophylactic administration in large quantities (10% of body-weight) of isotonic solutions of sodium salts, by mouth or intravenously, saves mice which otherwise die from the effects of burns or limb-ischæmia. The writer confirmed these results (unpublished). The results are not easily explained as simple fluid-replacement, and sodium depletion after injury may therefore prove to be an important factor in the development of shock.

Tissue-extracts

Watery extracts of many tissues given intravenously have a depressor action, and on this property many of the earlier claims of shock-producing extracts from traumatized tissues are based. With the advent of histamine, further search for a toxic factor in tissues appeared unnecessary. Moon was largely responsible for reviving interest in the toxic theory at a time when the histamine hypothesis was waning. He implanted minced muscle or liver into the peritoneal cavity, and the resulting shock was ascribed to the absorption of tissue-autolysates. Abraham, Brown, Chain, Florey, Gardner & Sanders (1941) repeated this work and found that death was due to clostridial infection. Sterile peptic digests of the tissue produced no shock. There is more recent evidence of the importance of infection in certain forms of experimental shock. Aub (1944) showed that death following the injection of a perfusate from ischæmic muscle was due to *Cl. welchii* infection and could be prevented by prophylactic antitoxin. Clostridia were found deep in the skin and muscle of normal dogs. Fowler (1944) found that death following the intraperitoneal implantation of muscle was due to *Cl. welchii* infection. Autoclaved muscle was

¹ [Gotzl, F. R. & Dragstedt, C. A., 1942, *J. Pharmacol.* 74, 33 observed that the blood of normal rabbits, when mixed with peptone *in vitro*, released a histamine-like substance.—Ed.]

much less effective, and even then, death, when it occurred, was due to infection. It would appear that ischaemic shock in dogs is, in large degree, due to infection. This may not be the whole story, even in dogs, for there is now evidence that normal muscle does contain factors capable of producing shock on injection.

Green (1943), following up preliminary studies on ischaemic shock in rats, renewed the search for a "toxic factor". It appeared that, however important local fluid-loss might be, it did not account for the whole of the shock syndrome. For this and other reasons, many attempts were made to prepare shock-inducing extracts from normal and injured muscle. The results were erratic but not uniformly negative. As extraction with boiling saline gave more uniform results, the possibility that the "toxic factor" might undergo rapid enzymic breakdown in dying muscle was considered. Following up a clue in the work of Dyckerhoff *et al* (Dyckerhoff & Schorcher, 1939, Dyckerhoff, Schorcher & Torres, 1939), enzyme-inactivation was attempted by rapidly immersing normal muscle in acetone. Saline extracts of the acetone ether-dried muscle from several species were found to contain a powerful vasodepressor substance. The most interesting finding was, however, that such extracts, when injected in several species by routes other than the intravenous, had no immediate depressor action, but instead consistently induced the gradual development of a prolonged shock-like state. A detailed comparison with ischaemic shock showed that, in many respects—particularly in the time of onset and degree of haemoconcentration, subnormal temperature, depressed renal function and the late fall in blood-pressure and respiratory rate—the two forms of shock were very similar.

Adenosine Triphosphate

Thinking that the "toxic" and depressor factors might be different substances, isolation of the depressor factor was attempted first, as there was biological evidence that it was an adenylic compound. Bielschowsky & Green (1943) fractionated the muscle-extracts, and a comparison of the cardiovascular effects of the purer fractions with those of adenosine triphosphate (ATP) showed a close similarity. This substance was finally isolated in large amounts from the acetone-treated muscle, and possessed not only the depressor but also the shock-inducing properties of the crude extracts. ATP rapidly disappears from dying muscle, and it appears that rapid immersion in acetone prevents its enzymic breakdown. This rapid breakdown probably accounts for previous failures to obtain "toxic" muscle-extracts (e.g. Wilson & Roome, 1936).

Green (1943) suggested that the intravenous lethal effect of ATP is due to circulatory failure, though in fact it may well be due to the immediate respiratory failure. The mechanism of shock-production following injection by other routes is more difficult to explain. The hypothesis advanced was that, whilst the depressor effect is primarily due to the adenosine radicle (Drury & Szent-Gyorgyi, 1929), the shock-inducing effect is due mainly to pyrophosphate. Bielschowsky & Green (1944) found that inorganic pyrophosphates, though not depressor, have rather similar shock-inducing properties. The pyrophosphate group, however, becomes more active in this respect when it is combined with adenylic or inosinic acids, particularly in the form of the magnesium salt. The relative independence of the depressor and "shock" factors is shown by the fact that de-aminated ATP (inosine triphosphate), whilst only slightly less toxic than ATP, has practically no depressor effect. The magnesium salt of ATP is the most active of the polyphosphates tested, and it is probably the form in which ATP normally exists in muscle.

Rabbit muscle after 3 hours' ischaemia contained only half as much active substance as normal muscle (Green, 1943). Bollman & Flock (1944) found in the rat that ATP-phosphorus disappeared from muscle at the end of 3 hours' ischaemia, and after 4 hours' ischaemia there was no local evidence of resynthesis for several days. They suggested quite logically that ATP is thus excluded as a factor in this form of shock. Green (1943) recognized this difficulty and pointed out that if synthesis of ATP began when the circulation returned it might leak out through the damaged cells as rapidly as formed. To support such a concept it would have to be shown that ATP-synthesis is possible under these conditions. (It is now known that such a synthesis is possible.) In any case, the biological effects may be produced by a

breakdown product and not by the intact substance. An amount of ATP roughly equivalent to that in the muscle involved in fatal ischaemic shock produces a comparable degree of shock. In both instances there is evidence of rapid ATP-breakdown, for the bulk of injected ATP has disappeared locally at a time when severe shock has yet to develop (Green, unpublished observations).

It is obviously necessary to find whether ATP is concerned in the pathogenesis of shock. There is a small amount of indirect evidence in previous work on adenylic compounds. Bennett & Drury (1931) obtained indecisive evidence of an increased release of adenylic compounds from the burned guinea-pig heart. Zipf (1931) identified the depressor substance in defibrinated blood as adenylic acid. He stated (1932) that the adenosine-equivalent of the blood is increased after a period of limb-ischaemia. Billings & Maegraith (1937), studying the role of histamine and adenine compounds in reactive hyperaemia, found a rise in the adenosine equivalent of venous blood returning from the rabbit-leg. Kellaway & Trethewie (1940) showed that *Cl welchii* toxin caused the liberation of adenylic compounds from perfused rabbit liver and cat-heart, a finding of possible interest in the previously mentioned relation of *Cl welchii* infection to ischaemic shock in the dog. More recently Stoner & Green (1944, 1945b) have shown in rabbits that, after limb-ischaemia, limb-trauma and severe dehydration and in "gravity shock", there is an early and often sustained rise in the adenosine-equivalent of the blood. In ischaemic and "gravity shock" they found suggestive, but by no means conclusive, evidence of a rise in blood-pyrophosphate. They also found (1945a) a rise in man following the application of tourniquets to both legs for 30 minutes. They gave ATP intravenously to men and found some features, particularly early bradycardia, similar to those following tourniquet release. Some tolerance to repeated doses of ATP occurred, and with it some diminution in the symptoms following tourniquet-release. These findings do not, of course, necessarily indicate a rise in blood-ATP, but only in nucleotide or nucleosides having the biological effects of adenosine. Owing to the small quantities involved, a purely chemical approach is difficult.

An interesting development of this work is the finding by Green & Stoner (1944a) that free magnesium potentiates the shock-inducing action of ATP and various related compounds including the non-phosphorylated compound, adenosine. In contrast, free magnesium reduces the depressor response to intravenous ATP, a finding which emphasizes the distinction between the depressor and shock-inducing properties of ATP (Bielschowsky, Green & Stoner, 1945). It was also shown that the general reaction to a variety of shock-inducing measures was increased following the injection of magnesium (Green & Stoner, 1944a). It was suggested that this effect might be due to the potentiation of adenosine compounds released from anoxic tissues. This hypothesis was supported by the finding that the effects of cyanide are potentiated by magnesium. Cyanide poisoning was shown to cause a rise in the adenosine-equivalent of rabbit-blood (Stoner & Green, 1945b).

What evidence is there of the role of ATP in traumatic shock? It is a physiological substance widely distributed in the tissues, which, on injection in many species, produces shock, so do histamine, adrenalin and insulin under certain conditions. Unlike the latter substances, however, it is rich in the tissue, i.e. muscle which, when damaged, is particularly responsible for the development of shock. There is some evidence that adenylic compounds are released from injured tissues, and that there is a close biological similarity between shock induced by ATP and by trauma. Whether it has a specific role in shock, or whether it is just one of the many substances capable of producing large-scale tissue-injury, is not yet known.

"Crush Syndrome"

It is not clear how far the "crush syndrome" in man has a direct bearing on the shock problem, though it provides a striking example of damage in an organ remote from the site of injury, probably produced by products of muscle-breakdown. This condition has been reviewed by Bywaters.* No one has succeeded in reproducing the entire syndrome

* [See article by Dr E. G. L. Bywaters (*BMB* 694) in this number—Ed.]

in animals, though in acute experiments a depression in creatinine-clearance has been observed in the first few hours following tight binding and trauma of the limb. Eggleton, Richardson, Schild & Winton (1943) and Corcoran, Taylor & Page (1943) have shown in dogs that, in a rather different type of injury, produced by partially-occluding tourniquets, there is a marked reduction in renal blood-flow, which they believe is due to circulatory vasoconstrictor substances. There seems little doubt that, following muscle-ischæmia, there is a diminution in renal function which may be independent of a fall in blood-pressure. Eggleton (1944) prepared, from ischaemic muscle, saline extracts which reduce creatinine-clearance by the kidney, and the substance responsible was thought to be an early breakdown product of protein, formed only during prolonged anaerobiosis. The injection of ATP also diminishes renal function in animals and, given intravenously in small quantities, it delays the onset of a water diuresis in man (Green, 1943, Green & Stoner, 1944b). The problem of traumatic anuria in man is, however, that of the identity of the factor(s) which produce early tubular damage of such severity that death, when it occurs, is due to renal failure. Bywaters & Stead (1944) produced fatal renal failure in rabbits with injections of myohaemoglobin, provided that the urine was as strongly acid as it is in traumatic anuria in man. The renal changes were

not, however, exactly similar to those seen in man. Myohaemoglobin greatly increases the nephrotoxic effect of ATP, though, again, the histological findings are not exactly those of the "crush kidney" (Green, 1943). It would seem that myohaemoglobin may play an important part in the renal damage, but the problem remains whether other muscle-products are concerned, and whether any of these are concerned in the earlier and more widespread features of traumatic shock. It seems to the writer that the "crush syndrome" may be a gross manifestation of the early renal failure seen in all types of shock. The kidneys are flooded with products of muscle-autolysis, following upon massive muscle-necrosis, and the already functionally-impaired tubules are thus damaged, often beyond hope of repair, before death from renal failure intervenes.

The physiological approach to shock has elucidated the all-important part that altered haemodynamics play.⁸ The later pathological approach has stressed the part of tissue metabolites in providing the exciting stimulus. The biochemical approach should dominate the next stage in its exploration of the chemical changes in injured tissues.

[See article by Dr J McMichael (*BMB* 693) in this number — Ed.]

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⁸ [BMB 717]

⁸ [BMB 714]

PRESENT STATUS OF THE CLINICAL PROBLEM OF "SHOCK"

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The views generally held at the beginning of the present war may be stated very simply. It was thought that shock was a result of depletion of the effective volume of blood in circula-

tion. As a result of decreased filling of the heart, the cardiac output is lowered to a level at which cardio-acceleration and vasoconstrictor reflex no longer "compensate" and the

blood-pressure falls. This "classical" concept still holds true, but as a result of much research it has undergone modification, and we may consider *seriatim* the basic points.

I. Blood-volume Reduction

The view that blood was pooled or trapped in some part of the vascular system has been discarded. It is now widely agreed that haemorrhage is the major factor producing shock in war wounds. Haemoconcentration, indicating plasma leakage from capillaries, is not seen except in burns and crushing injuries and some types of abdominal injury. The efforts made by various experimental workers to reproduce haemoconcentration as an essential factor of shock seem to have been misguided. Much misunderstanding seems to have arisen in the past as to the rate at which blood is diluted after haemorrhage. The work of Wallace & Sharpey-Schafer (1941) has made it clear that full blood-dilution is not reached until some 40 hours have elapsed after the loss of 1000–1200 cm³ of blood. The usual degree of dilution seen an hour or two after severe blood-loss is seldom more than 15–20%, i.e. the haemoglobin is reduced to 80–85% of the original value. Post-haemorrhagic anaemia is thus not recognizable by ordinary haematological methods until two or three days have elapsed. In the 1914–18 war these phenomena of bleeding were not generally appreciated, though the importance of haemorrhage as a cause of shock was recognized by Keith and a few other clinical observers.

The quantitative estimation of blood-volume reduction after haemorrhage is still beset with difficulties. It is reasonably certain that 60% of the blood-volume may be lost in some cases, and such patients may recover after massive transfusion. Dyes which are used for blood-volume estimation are admittedly lost from the circulation, and the rate of loss is variable in cases of traumatic shock (Bowler, Crooke & Morris, 1944). The dye method may over-estimate the blood remaining in circulation after haemorrhage. It has been shown that it over-estimates blood-volume even in the normal subject (Hevesy, Koster, Sorenson, Warburg & Zerahn, 1944).

Using a concentrated-corpuscle method, McMichael, Sharpey-Schafer, Mollison & Vaughan (1943) found that blood-volumes were often severely reduced in chronic anaemia. This state of affairs was subsequently found to be associated with an *increased* cardiac output (Sharpey-Schafer, 1944). This *hyperkinetic* circulatory state may develop about 24 hours after haemorrhage has taken place, and it is in fact very frequently observed in patients admitted to hospital with gastro-intestinal bleeding. This series of observations makes it clear that while *acute* reduction of blood-volume may induce "shock," slower reduction (subacute or chronic) leads to no such state. If there is recovery from the initial collapse after haemorrhage, the hyperkinetic state may ensue in a matter of hours. The mechanism of this circulatory adaptation to a low blood-volume is not understood. It does, however, open up the possibility of a pharmacological approach to the problem of treatment of haemorrhagic shock.

II. Cardiac Output and Peripheral Vascular Resistance

The remarkable advance in technique of cardiac-output determination introduced by Cournand & Ranges (1941) has rendered possible a quantitative estimation of peripheral arteriolar resistance as well. Mean arterial pressure (BP) is proportional to the resistance to flow imposed by arteriolar tone (TPR) and also to the volume of blood ejected into the arteries in unit time, or the cardiac output (CO). Thus $BP \propto CO \times TPR$. If BP and CO are known, TPR-changes can be followed.

In haemorrhage, the initial changes indicated by the "classical" concept are confirmed. The pressure falls in the great veins near the heart, the cardiac output falls, the pulse is accelerated and the peripheral resistance is increased. After this first phase, however, further reactions may develop which are rather unexpected. The blood-pressure, which was at first maintained, gives way and falls to levels of the order of 60 mm Hg. The pulse, after initial acceleration, falls from 90 to 40–50 per minute. This *vaso-vagal reaction* is due to a sudden vasodilatation in the arterioles of the skeletal musculature. The peripheral vasodilatation is mediated by autonomic nerves, as the reaction is abolished in the forearm-muscles by blocking the main nerves at the

bend of the elbow (Barcroft, Edholm, McMichael & Sharpey-Schafer, 1944).

This reaction, though resembling an ordinary faint induced by emotion, seems to bear some relation to the volume of blood lost. Its incidence rises from about 4% among blood donors bled 420 cm³ to 40–50% of those bled a litre or more. Most reflexes seem to be protective, and a purposive interpretation can usually be offered. If the vaso-vagal reaction is indeed a reflex, its usefulness to the bled individual is difficult to appreciate. The reaction may even be precipitated during anaesthesia in an injured person, especially when a fracture is manipulated. Placing a wounded soldier in the sitting position may also induce vaso-vagal syncope. It has even been suggested that vaso-vagal syncope may be fatal, while this is possible, it is difficult to substantiate, as we know little of the meaning of slow heart-rates in the moribund.

Recognition of vaso-vagal collapse is easy if the slow heart rate is observed. Recovery in mild cases will occur when the recumbent or head-down position is adopted. Methedrine (N-methyl amphetamine) 20 mg intravenously, or 30 mg intramuscularly, accelerates recovery. In those who recover without drug-treatment, the pulse often remains slower than would be expected for the degree of blood-loss. Thus the vaso-vagal factor may complicate and modify the classical picture of oligaemic shock. Perhaps this point is best illustrated by a case observed recently by the writer.

Following a flying-bomb incident, a middle-aged patient was admitted to hospital with injuries from flying glass, including deep cuts from which blood-loss had been considerable. Two hours after the injury the arterial pressure was 65/40 mm Hg and the pulse-rate 80 per minute. The heart-rate was thus unexpectedly slow in relation to the blood pressure. 20 mg methedrine was given intravenously, after which the blood-pressure rose to 90/60 and the heart rate rose to 110. It seems possible that methedrine abolished the vaso-vagal component and restored the "classical" state of affairs.

Vasodilator factors are certainly being more widely appreciated in the condition following injury. In his recent Harvey Lecture, Richards (1944) has shown that, in the average case of "shock," the cardiac output seldom falls below 3 litres per minute. Yet this degree of cardiac-output reduction may be reached in simple mild haemorrhage and the arterial pressure may remain high as a result of "compensatory" vasoconstriction (McMichael & Sharpey-Schafer, 1944). Vasoconstriction thus seems to be inadequate when the fully developed shock-picture is present. In other words, the deep fall in blood-pressure is due more to lack of vasoconstriction than to a further fall in cardiac output. It is not suggested that the vaso-vagal reaction is always the responsible vasodilator mechanism. Other factors such as infection and tissue-trauma, with local or general vasodilator effects, may come into play, but as yet these influences are poorly defined.

III. Tissue Anoxia

It is generally thought that the circulatory failure of "shock" produces final dissolution by diminished oxygen transport to the tissues. It was believed that oxygen therapy might find a place in increasing slightly the amount of available oxygen in each unit of blood reaching the tissues. This expectation has not been fulfilled, and a paper by Frank & Fine (1943) gives much food for thought. Dogs shocked by bleeding were given oxygen even under high pressure (up to 3 atmospheres). By this means it was hoped to compensate for any deficiency in oxygen-supply due to sluggish blood flow. Yet the survival-rate of the animals was uninfluenced, and the oxygen-uptake by the tissues could not be increased. It seems likely, therefore, that considerable areas of the vascular bed are completely shut off in profound shock, a state of affairs which was demonstrated many years ago in bled animals by Rous & Gilding (1929).

IV. Circulatory Reactions other than those due to Haemorrhage

Thus far we have dealt particularly with the circulatory sequelae of haemorrhage. Other types of injury may lead to oligaemia, especially burns and crushing injuries, which produce haemoconcentration and local loss of fluid into the traumatized areas. Detailed discussion of these topics is beyond the scope of this brief review. A practical point in the management of the depressed circulation in such cases is

that serum transfusions have to be maintained for many hours, as leakage of plasma fluid may be continuous for a long time, and the infused serum thus may be lost from the circulation

When injury is complicated by bacterial invasion with toxæmia, another "shock"-producing factor is introduced. The factors concerned here still require close analysis by modern methods. Richards (1944) has shown that in belly-wounds, when infection is a frequent complication, the cardiac output is very low in relation to the blood-volume, which is only slightly reduced. This suggests, either that the heart is directly damaged by the bacterial poisons, or that the mechanisms regulating cardiac filling during diastole have broken down. Richards' right-auricular-pressure measurements suggest that the latter mechanism is responsible. In cases dying of bacterial toxæmia with circulatory collapse, Rich (1944) has shown that the suprarenal glands have undergone degeneration in the cortical zone.

Discussion of bacterial toxæmia brings us to the edge of the subject of circulatory collapse in civil medicine. Since it has been shown that a chronic reduction in blood-volume in anaemia may be accompanied by a high cardiac output, it becomes difficult to accept the common explanation that the circulatory collapse of crises of Addison's disease is due to a low blood-volume.

What has the suprarenal cortex to do with the maintenance of vasomotor or venomotor tone? While suprarenal-cortical extracts have been found of little value in traumatic shock, the observations of Richards and of Rich open up the possibility that in overwhelming infections regulation of venomotor tone may be impaired and a suprarenal-cortical mechanism may be involved somewhere in the chain of events.

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Other types of non surgical shock require a new approach by the methods now available. The collapse of diabetic coma and that of coronary thrombosis await analysis by the new techniques, and we may be certain that much new light will soon be cast on these problems.

"Irreversible Shock"

Even after adequate transfusion, some cases of wound-shock may fail to recover. In clinical practice, many such cases result from unrecognized complications such as fat embolism, visceral injuries, etc. Blalock (1934), however, found that even after simple haemorrhage in animals, a blood-pressure left too low for too long would not recover, even after replacement of all the lost blood. The cause of this irreversible state is uncertain. Wiggers & Werle (1942) suggest that the heart has suffered, perhaps from long-diminished coronary flow. Engel, Harrison & Long (1941) have concentrated recently on the effects of haemorrhage on liver-metabolism. The liver, being dependent for its oxygen supply more on the portal venous than on hepatic arterial blood-flow, is apt to suffer considerably when the general circulation-rate is depressed, as in shock (McMichael, 1938). Blood amino-acids increase considerably in the blood of animals in haemorrhagic shock, and this accumulation is dependent partly on a poor hepatic blood-flow. The significance of these metabolic changes in the development of the "irreversible state" is not known, this work, however, indicates the lines along which fruitful studies on the metabolic consequences of haemorrhage may be made.

[Readers interested in this subject should refer also to a previous article on *Circulatory dynamics of haemorrhage* by Dr E. P. Sharpey-Schafer (*BMB* 425)—Ed.]

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ISCHAEMIC MUSCLE NECROSIS ("CRUSH SYNDROME")

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During the 4½ years' aerial bombardment of Britain, a condition previously unrecognized here, resulting from burial beneath masonry and rubble for several hours, became well known in the hospitals of the most severely-hit districts. It was known at first as "crush injury" (Bywaters & Beall, 1941) or, variously, as "traumatic oedema", "traumatic anuria", "compression syndrome", etc. Later, with the realization that muscle damage played the major role in its pathogenesis, the title "ischaemic muscle-necrosis" was suggested (Bywaters, 1944).

The condition, however, had been partially described 25 years before, during the 1914-18 war, by Frankenthal (1916) and, following him, by others. Minami in 1923 adequately summarized and discussed the facts known up to that time. From then until this present war, no mention of it seems to have been made, which is rather surprising since ischaemic muscle-necrosis does occur in civil life, admittedly somewhat rarely, as the result of industrial, traffic and mining accidents. We have seen, and McLelland (1941) and Caplan & Dunkerley (1945) have published, cases where prolonged pressure due to a fall of stone in a mine has produced a sequence of events exactly similar to that occurring in air-raid casualties. It has also resulted from "soft" compression, in a shelter disaster where over 200 civilians were jammed together and on top of each other

on a flight of stairs for just over 2 hours (Bywaters, Crooke & Morris, 1943).

Quite apart, however, from compression, cases of anuria occur following vascular injuries or fractures sustained in battle and civilian accidents (Darmady, Siddons, Corson, Langton, Vitek, Badenoch & Scott, 1944, Parsons, 1945). Many of them, apparently due neither to sulphonamide nor to mismatched transfusion (Husfeldt & Bjerring, 1937, Bywaters, 1942, Belsey, 1942, Graham, 1942, Magner, 1942, Williamson & Janes, 1942, Glen, 1941), show the same pathological lesions as are seen in crush injury—including ischaemic muscle necrosis and, in a number of such cases, muscle pigment has been identified in the urine. Muscle pigment has also been found in the urine following spontaneous thrombosis of the femoral artery (Bywaters, 1945). It seems therefore that "ischaemic muscle necrosis" is a better title than the earlier ones since it includes these other cases where ischaemia results not from prolonged pressure but from arterial spasm, rupture or occlusion.

The incidence of this lesion in air-raid casualties lies between 1% and 5%—the figures from various hospitals vary somewhat, perhaps because of the types of building in the locality, perhaps because of the differences in diagnostic criteria.

Clinical Aspects

Muscle necrosis should be suspected in any case with a history of burial beneath debris for 2 hours or more,

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that is, any case admitted to hospital well after the first flood of casualties from the same "incident". Examination immediately after admission may reveal very little, since the characteristic pressure-erythema outlining the compressed areas will usually develop only after the patient has warmed up in bed. This erythema may be followed by blister-formation, often erroneously thought to be due to burning. In other instances, areas of pallid grey skin-necrosis surrounded by erythema have also closely simulated burns. Care should be taken to examine closely the buttocks and back, as lesions in those sites are easily missed. Local anaesthesia and paralysis of the affected muscle-groups are present, but pain is rare. Patients compressed for less than 2 hours seldom show local damage or general ill-effects (unless arterial spasm prolongs the ischaemia), as muscle will survive under anaerobic conditions up to that time without irreversible change. Burial for periods longer than the minimum necessary for muscle death does not seem to enhance the severity of the condition: this is determined by the extent of muscle necrosis. Those patients with a large amount of muscle damage may appear comparatively well on admission but, within a few hours, their condition rapidly deteriorates. Plasma leaks out through the damaged capillaries into the necrotic muscle, the limb swells, and haemoconcentration develops. While the blood-pressure may be well maintained for some time, as in burns, perhaps due to the increased viscosity associated with haemoconcentration, a point is reached where vasoconstriction no longer compensates for continued plasma loss: there is a sudden fall of blood-pressure, often precipitated by anaesthesia and heat. This fall of blood-pressure should be forestalled by the administration of saline and lactate solution by mouth or parenterally, reinforced with plasma. Plasma is the fluid to use when blood-pressure has already fallen: dosage should be regulated by the response of systolic and venous pressures. The latter, observed in the neck-veins by Lewis' method, will rise only with over-transfusion, except in rare instances, associated usually with pulmonary fat-embolism or myocardial infarction.

The majority of patients recover from this "shock" phase, if they have been adequately transfused, within the first 18 hours. "shock" can usually be accounted for by the local fluid loss: it is of the same order of clinical severity as that due to loss of equivalent amounts of blood. This is of great interest, as the toxæmic theory of the origin of post-traumatic "shock" still has its proponents (see Wiggers, 1942 and Green, 1945). Such toxins are thought to come from necrotic or damaged tissue, yet in this type of injury, where 1-2 kg of necrotic tissue may give up their intracellular contents to the blood-stream within 24 hours, there is usually little difference in the general condition during the first few days from that seen after a severe fracture, with an equivalent decrease in blood-volume due to haemorrhage and perhaps about 50 to 100 g of necrotic tissue.

Unlike haemorrhage, however, plasma leakage begins and ceases only gradually. The affected limbs become swollen and brawny: peripheral arterial pulsation may disappear, perhaps due to increase of pressure in the deep compartments. The circulation may return spontaneously, or after incision of the deep fascia with release of tension. In patients that recover, some function will return to partially-damaged muscle when the oedema subsides: large volumes of necrotic muscle, however, do not regenerate, but undergo fibrosis similar to that of a Volkmann's contracture (Bradley, 1942). All such affected muscles need splinting during the phase of fibrosis. Infection rarely occurs, but late calcification has been recorded by Albert & Mitchell (1943) in the only English case from the 1914-18 war.

Renal Damage

The first urine passed may be normal (representing urine secreted before the period of burial), later urines, however, are highly acid (pH 4.8 to 5.6) and contain albumin, creatine and muscle pigment (Bywaters, Delory, Rimington & Smiles, 1941). If renal failure has set in (and this may occur very early, soon after release from debris), the urine is scanty, of low specific gravity, and contains only little pigment, mostly in the brown deposit, as acid haematin: the supernatant may appear quite clear, but spectroscopic examination of a thick layer will usually show the bands of

oxy- or met-myohaemoglobin. The composition of the urine tends towards that of glomerular filtrate: the urea concentration decreases, that of chloride may rise towards the end even with low plasma-levels, but, except in the initial stages, no reducing substances are found. Towards the end of the first week the daily output may increase and also the urea concentration (Beall, Bywaters, Belsey & Miles, 1941), but unless a large diuresis sets in at this time the patient will die at about the 6th to 7th day with nitrogen and potassium-retention. In patients who develop renal failure and recover (Belsey, 1942, Longland & Murray, 1941, Blackburn & Kay, 1941) albuminuria lasts longer than pigment excretion: function will return to normal within about 6 months. If renal damage has been prevented, the urine is less acid (pH 6 to 8), without deposit and of a bright red colour due to the presence of oxymyohaemoglobin in solution. Very mild cases show merely a trace of pigment, albumin and creatine with no depression of renal function.

Pathology

In a typical case dying on the 6th day, the affected limb contains much serous fluid in the subcutaneous planes, seeping through from the underlying muscle. The muscle itself is wet and swollen, bulging out immediately the fascia is incised, usually rather opaque and friable and of a peculiar grey-white colour, marked sometimes by small haemorrhages—the so-called "fish-flesh" appearance characteristic of Zenker's degeneration. There is a sharp boundary zone between living and dead muscle: it is here that calcification of the dead fibres first occurs. Microscopically the dead fibres lose their nuclei: cross-striation is retained except in the boundary-zone where waxy degeneration and, on the more normal side, vacuolar degeneration occur. Later, macrophages surround the injured fibres and regeneration occurs at the periphery from surviving sarcolemmal cells.

The liver appears normal but microscopically shows many mitoses (up to 9 per thousand cells) if the patient has survived 5 days or more. These may or may not be associated with small necrotic areas with a paracentral or mid-zonal distribution in the lobule, probably related to the initial period of hypotensive "shock".

The kidneys on the 6th to 7th days (Bywaters & Dible, 1942) are swollen, with a pale, oedematous cortex and often a pigmented medulla. Microscopically, Bowman's capsule contains eosinophil debris probably from the first convoluted tubule, which is catarrhal and drawn up into the neck of the capsule. The second convoluted tubules and collecting tubules contain pigment. In the boundary-zone, and particularly in the neighbourhood of connective-tissue septa, casts are seen lying free in the oedematous interstitial tissue, extruded from ruptured and partially-damaged tubules of the thick part of Henle's loop. They may further rupture into veins (Dunn, Gillespie & Niven, 1941). Morison (1941), describing 3 cases, noted the resemblance to the renal lesion of myelomatosis, and stressed the obstructive nature of this change.

These changes are also seen after intravascular haemolysis; Baker & Dodds (1925) showed, in rabbits injected with haemoglobin, that renal failure will ensue only if the urine is acid. They advanced the hypothesis that renal damage was due to mechanical blockage of the tubules by precipitated acid haematin or methaemoglobin, and initiated the use of alkalis for prevention. A similar picture, except that pigmented casts were absent, has been seen (Bywaters, unpublished data) in acute hydronephrosis due to neoplastic blockage of the ureter, and in sulphapyridine tubular blockage (see also Maisel, Kubik & Ayer, 1944); we interpret this damage, therefore, as a sign of increased intra-renal pressure, the anatomical counterpart of the tubulo-venous and pyelo-venous backflow shown functionally by Hinman (1934). In the early stages of crushing injury, this change is absent.

Pathogenesis

A picture similar in many ways to that seen clinically in crush syndrome can be produced in the rabbit by winding rubber tubing tightly over the thigh (Bywaters & Popják, 1942). If compressed for over 2-3 hours, the underlying muscle becomes necrotic. Immediately after release, plasma leaks out through the damaged capillaries, the limb swells, haemoconcentration develops and is accompanied, if of severe degree, by a fall in blood-pressure. The severity of

the lesion is proportional to the extent of muscle damaged. But, although there is usually a rise in blood-urea, this is not high and no irreversible renal damage results. Creatine appears in the acid urine, and occasionally traces of protein, but no pigment. This is because the muscles compressed contain no myohaemoglobin. Analysis shows, however, that they lose, within 2 hours, most of their creatine, potassium and phosphorus content.

If a solution of human myohaemoglobin is injected at the time of release, renal failure may result (Bywaters & Stead, 1944). Renal failure may also result from myohaemoglobin-injection alone in an animal previously rendered acidotic by ammonium chloride. This work on rabbits splits the problem of pathogenesis in man, therefore, into two parts for consideration: the initial phase of plasma loss, and the later phase of renal failure. The former aspect has been investigated experimentally in many species (Wilson & Roome, 1936; Duncan & Blalock, 1942a, 1942b; Duncan, 1943; Green & Bergeron, 1945; Ashworth, Jester & Lloyd-Guy, 1944; Canzanelli, Guild & Rapport, 1945; Rosenthal, Tabor & Lillie, 1945; Bollman & Flock, 1944; Root & Mann, 1941; Warren, Merrill & Stead, 1943; Blalock, 1943; Aub, Brues, Dubos, Kety, Nathanson, Pope & Zamecnik, 1944), but the mechanism of the latter process is still somewhat obscure. Experimental work has shown in the dog that a depression in creatinine-clearance followed binding and trauma, but Eggleton, Richardson, Schild & Winton (1943) concluded that this was not due to blockage. Eggleton (1942) found that the liver was able to "detoxicate" blood returning from the damaged limb. Bing (1944) showed that renal failure followed the infusion of methaemoglobin in acidotic but not in normal dogs: it was characterized by a fall in effective renal plasma-flow, filtration-rate and tubular resorption. No impairment was found in acidotic dogs given myohaemoglobin. The lesion produced in rabbits by Scarff & Keele (1943) by temporary occlusion of the renal artery was characterized by first-convoluted-tubule damage; this is not seen in human crush syndrome.

Summarizing, the renal lesion is associated with the excretion of pigment and other breakdown-products of muscle in an acid urine: in the late phase there are signs of tubular blockage, although Bywaters & Dible (1942) and many others, e.g. DeGowin, Warner & Randall, 1938, before them with reference to the "haemoglobin kidney", have doubted whether enough pigment is present in the tubules to obstruct mechanically the passage of urine. It seems possible that damage done to tubules in the early stages may hinder re-absorption with an acute rise in intra-renal tension and blockage of a functional rather than a mechanical nature.

Treatment

As renal failure, once developed, is very resistant to treatment, the first aim is to prevent its development. From the outline of pathogenesis given above, it is evident that this should be attempted:

- i by preventing any fall in renal blood-flow. Prompt restitution of lost plasma and extracellular fluid by transfusion of plasma and crystalloid solutions such as saline or lactate is indicated;
- ii by maintaining a high rate of flow of dilute alkaline urine. This is best done by forcing fluid by mouth from the earliest possible moment as a first-aid measure. Sodium bicarbonate, 1 teaspoonful to the pint [about 1 teaspoonful per $\frac{1}{2}$ litre], should be repeated hourly. Hydration and alkalization can be most rapidly achieved in hospital by the intravenous route, isotonic (1.87%)

sodium lactate being used together with glucose-saline. If a diuresis is not soon obtained, renal damage is probably already present, and further forcing of alkali and fluid is then dangerous, since alkalosis develops readily in patients with renal failure. The reaction of the urine changes from acid to neutral only slowly when renal function is impaired, if, therefore, an alkaline diuresis is not obtained in the first 12 hours despite reasonable alkali therapy (normal people need about 30 g of sodium bicarbonate in 24 hours to retain alkalinity) it should be stopped. In successful cases, alkali should be given at a rate just sufficient to keep the urine alkaline for as long as pigment is being excreted (24 to 48 hours). Such treated cases, of a severity more than sufficient to produce high grade renal failure if untreated, will put out large quantities of muscle pigment, etc., without developing any nitrogen retention.

The use of citrate to produce alkalization is not without danger on account of its calcium-binding property. In an emergency 500 cm³ given slowly intravenously has not had ill-effects. Whether given by mouth or by other routes, care should be taken that the salt is that of sodium, not of potassium, since potassium poisoning is easily produced in the uraemic state (Finch & Marchand, 1943). Indeed, some of these patients with uraemia show, spontaneously, signs of potassium intoxication due to resorption from damaged muscle (Beall, Bywaters, Belsey & Miles, 1941).

While most deaths before the 6th day are due to failure to transfuse plasma, or to associated injuries, some have been due to overloading the circulation. Watch should therefore be kept on the neck-veins and the lung-bases.

The use of pressure-bandages to limit plasma loss in the limbs has been advocated (Patey & Robertson, 1942; Duncan & Blalock, 1943). There seems no advantage over giving plasma intravenously, and indeed it is potentially dangerous, as in some cases the increase in intra-muscular pressure, probably osmotic, due to autolysis, is itself adequate to obliterate traversing blood vessels against the encircling fascial sheaths (Belsey, 1942). Tight binding would only increase this tendency.

The injured limb, if at all ischaemic, should be kept cool, rather than, as so often happens, heated. This will decrease the rate of autolysis and also allow living tissue to survive on a smaller margin of blood supply (Allen, 1941). Cooling is ineffective if reactionary hyperaemia has occurred. Immobilization is also needed, as Bollman & Flock (1944) have shown that splitting of phosphocreatine and decrease in adenosine triphosphate occurs much more rapidly with exercise of the ischaemic limb.

In the treatment of established renal failure, sodium sulphate and many other drugs have been used without signal success. Sometimes spontaneous recovery occurs, and then the treatment in use at that time is thought responsible. Theoretically, decapsulation should be successful. In practice we have not found it so. Renal failure of this type is eminently suited for trial of artificial kidneys (Kolff & Berk, 1944), as severely affected kidneys have sometimes shown a complete spontaneous recovery (Belsey, 1942).

While we may hope that this and other types of injury from "enemy action" will not recur, cases with an apparently similar mechanism will continue to appear, as the result of accident, intravascular haemolysis, etc. It is hoped that the impetus given by war to this aspect of muscular and renal pathology will be maintained, as much more experimental work is required for the adequate understanding of this condition.

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¹ [BMB 717]

REVIEW OF SELECTED PAPERS

Wound Healing

The four reviews in this section are concerned with experimental studies. An interesting symposium on the surgical treatment of wounds has been published in two recent (12 May and 19 May, 1945) numbers of the "Lancet". Titles and authors of these papers are indexed in the "Guide to the Journals" in this number of the Bulletin (BMB 720)

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SYMPOSIUM ON WOUND HEALING

[This is a report, not before published, by Dr A Glucksmann. A longer report by Mr P B Medawar and Dr F H K Green was published in the *Bulletin of War Medicine*, 1944, 4, 251-257.—ED.]

The Society for Experimental Biology held its 55th conference in Cambridge from 22-24 September, 1943, and devoted the meeting to a symposium on wound healing in which clinicians and laboratory workers took part.

Three introductory papers were read to provide a common basis for discussion. They were followed by contributions under the following headings

- i systemic effects and biochemical changes in injury and repair,
- ii wound healing in brain and nerves,
- iii problems of grafting, of skin wounds and scars,
- iv control of wound infection

In his introductory paper on the clinical aspects of wound healing, Professor J Patterson Ross (St Bartholomew's Hospital, London) stressed the importance of systemic factors (such as age of patient, state of general health, adequacy of diet) as well as local factors (such as infection, site of wound, mechanical stresses and vascularization) in the normal process of wound healing. In cases of delayed healing the disturbing causes should be looked for and remedied rather than that growth-promoting substances should be applied indiscriminately.

Mr E N Willmer (department of physiology, Cambridge), dealing with the cellular aspects of wound healing, emphasized the correlation between the regeneration of connective and epithelial tissue in normal wound repair. He showed that stimulation of connective-tissue regeneration for instance might result in collagen fibre hypertrophy and inhibit epithelial regeneration. Substances applied for the purpose of promoting wound healing or controlling wound infection should be tested for their differential effect on the regenerating tissues so as to avoid interference with the proper correlation of the repair processes.

Dr L J Harns (Sir William Dunn Nutritional Laboratory, Cambridge) surveyed the influence of vitamins on wound repair. Vitamin D is important in the healing of fractures, C influences the tensile strength of scars, K has been shown to prevent post-operative haemorrhage in obstructive jaundice. The other vitamins do not seem to play a role of specific importance in wound healing. The action of vitamin D was described as exerting "chemical control" of the calcium salts reaching the prepared matrix and of their deposition. Vitamin C exerts a "cytological control" by enabling formative cells to maintain their functional activity. In complete deficiency, such cells (odontoblasts, ameloblasts, osteoblasts, fibroblasts, etc) fail to lay down new tissue. In partial deficiency, the later processes involved in tissue formation may be inhibited while the earlier phases may proceed normally or be exaggerated.

Systemic effects and biochemical changes

Lieut J M Barnes (R A M C) discussed the reflex arterial spasm following injuries and warned against interference with wound circulation by therapeutic means.

Dr D P Cuthbertson (department of physiology, University of Glasgow) based his observations on clinical experience with patients suffering from fractures and on animal experiments. After a short interval, fracture of bones is followed by a "flow-period" which reaches a maximum towards the end of the first week and is characterized by a marked loss of nitrogen, sulphur, phosphorus, and potassium. The nitrogen loss amounting to about 20 g daily cannot be balanced by increased protein intake, but is prevented to some extent by the injection of a crude extract of ox anterior pituitary gland or of testosterone. In recent experiments with Munro the author found that in rats maintained on a protein-free diet before and after injury, the nitrogen excretion was not increased. It thus appeared that protein inanition had reduced the metabolizable protein store. In spite of this lack of dietary protein, skin wounds in rats healed, while injection of pituitary extract, though preventing excessive nitrogen loss, did not significantly affect the rate of healing of rat wounds. He found evidence, however, that the mean time required for the healing of skin wounds in rats was significantly reduced when the animals were given dried thyroid or the appropriate dosage of 2-4 α -dinitrophenol.

Mr E J Clark & Dr R J Rossiter (department of biochemistry, Oxford), investigating the biochemical effects of burns in rats and rabbits, found a rise in the blood lactic-acid and a fall in the glycogen content of the whole carcass. These changes could be imitated by adrenaline injection and could not be obtained after the adrenal gland had been removed. Changes in nitrogen metabolism following burns were found

to be very similar to those described by Cuthbertson in fractures

Dr E. Kodicek & Dr P D F Murray (Sir William Dunn Nutritional Laboratory, Cambridge and department of biology, St. Bartholomew's Hospital Medical College, London) observed the following changes in guinea-pigs kept on a diet partially deficient in vitamin C (i) a very marked subperiosteal hyperostosis of the tibia and fibula combined with a typical scurvy porosis of the original bone, (ii) oedematous swelling of the leg-muscles combined with a marked increase in numbers of fibrocytes and the formation of a delicate fibrillar stroma, accompanied by fibre dissolution in periosteum, interosseous membrane and fascias, and by muscular atrophy, (iii) ankylotic changes in the knee-joint due to a formation of a highly cellular and thin-fibred connective tissue combined with necrosis of the synovial membrane and thinning of the articular cartilage. These changes could be attributed to the failure of vitamin-C-deficient animals both to maintain and to form properly such mesenchymal structures as bone, cartilage, periosteum and collagenous and muscle fibres, while the initial processes of cellular proliferation and formation of a fine-fibrillar stroma were actually increased in partial vitamin-C deficiency

Dr G H Bourne (department of physiology, Oxford) examined the process of repair of bone injuries (i.e. holes bored through the cortex into the medulla) in animals kept on diets completely or partially deficient in vitamin C. A positive correlation was found between the amount of vitamin C in the diet and the qualitative and quantitative progress of bone repair

Dr H. B. Fell & Dr J F Danielli (Strangeways Research Laboratory and department of biochemistry, Cambridge) studied the distribution of alkaline phosphatase in standard rat wounds and burns at different stages during the repair, using Gömöri's histochemical method. Shortly after injury the infiltrating polymorphs only and the scab gave a really intense reaction. With the beginning of fibre-formation the fibroblasts and the newly formed thin intercellular fibres were found to contain considerable amounts of phosphatase. After the formation of thick fibre bundles in the fully-developed scar, the phosphatase reaction declined and disappeared

Wound healing in brain and nerves

Dr D S Russell (department of neurosurgery, Oxford), dealing with observations on patients suffering from brain injuries and with animal experiments, stressed the similarity in the fundamental repair processes in the brain and in other tissues. The initial necrosis attending brain injuries might, however, be very great owing to the superficial localization and great vulnerability of cerebral vessels. Gross distortion of the brain and the ventricular system were late sequelae of extensive injuries and should be distinguished from traumatic cysts due to cerebral herniation. For the treatment of brain injuries, penicillin solutions, powders of sulphanilamide, sulphapyridine and sulphadiazine, as well as dilute, isotonic, buffered solutions of proflavine, were used without harm to the brain tissue. Acridine compounds used as powders caused extensive necrosis

Dr A. H. S. Holbourn (department of physiology, Oxford) considered that shear-stresses were the forces ultimately responsible for mechanical brain injuries. Cysts or glial scars were found to occupy the calculated areas of highest shear-stresses

Mr J Z. Young (department of zoology, Oxford) analysed the colloid-chemical forces involved in nerve injury and repair. After severing a peripheral nerve the fibres in the distal stump shortened, formed spirals and degenerated owing to a disorientation of long protein molecules in the axoplasm. In the central stump on the other hand the axoplasm swelled and poured forth from the cut end to form small fibres on suitable surfaces such as Schwann cells. Turgor-pressure emanating from the cell body combined with the presence of suitable restrictive surfaces (nerve sheaths) could explain these findings and might be responsible for the maintenance of normal axoplasm organization

Mr M. Abercrombie (department of anatomy, University of Birmingham) discussed the relation of cell-movement to cellular proliferation in severed nerves with the tissue-culture technique.¹

¹ [see BMB 132.—Ed.]

Problems of grafting skin wounds and scars

Mr R. Mowlem (Hill End Hospital, St Albans) showed some striking clinical results in bone injuries obtained by grafting loosely-packed chips of cancellous bone. Such grafts healed soundly and promptly, were easily orientated, and showed little tendency to necrosis and subsequent infection. The grafted pieces of cancellous bone were able to survive, as they were not damaged in preparation. Such damage was found unavoidable in obtaining the usual "saw-cut" splinters of compact bone. Furthermore the endosteal tissue in the small pieces of cancellous bone not only survived but participated in the regeneration of bone and helped to join the various fragments

Mr J N. Barron (Hill End Hospital, St Albans) discussed various factors involved in the successful taking of skin autografts, such as control of infection, vascular and mechanical conditions of the graft-bed, and the nutritional state of the patient, in relation to the underlying biological principles. He could base his observations on 800 cases of plastic repair and was able to show most interesting illustrations of the adaptability of grafts and of the return of function and sensation in them

Mr P B. Medawar (department of zoology, Oxford), working with Dr Gibson on problems of human auto- and homografts, accounted for the failure of homografts in man and mammals by assuming the development of active immunity in the recipient

Dr A. Glucksmann (Strangeways Research Laboratory, Cambridge) found hypertrophy of scars and formation of scar keloids in 70 of Mowlem's and Barron's cases to be due to a peculiar type of foreign-body reaction which tended to spread as perivascular infiltration with subsequent fibrosis. This reaction was caused most frequently by intrinsic "foreign" bodies such as dislocated hairs or follicles. Intradermal autografts of rat skin (made in collaboration with H B. Fell) showed that free hairs and keratin elicited a similar reaction with spreading perivascular infiltration and fibrosis. The thin fibred perivascular tissue was slowly transformed into dense hyalinized connective tissue typical of keloids. Hypertrophy of scars and scar keloids were interpreted as fibrosing granulomata rather than true fibromata.

Professor G R. Cameron (department of pathology, University College, London) showed slides illustrating the effects produced by various chemical burns and the subsequent repair

Control of wound infection

This last group of papers needs only summary mention in view of the reports previously published in the Bulletin.

Dr F. Hawking (National Institute for Medical Research, Hampstead) gave a survey of the pharmacological properties of sulphonamides.²

Dr E. Chain (department of pathology, Oxford) reviewed the history of the development, purification and chemistry of penicillin.³

Dr M E. Florey (department of pathology, Oxford) described some of the striking clinical results obtained with penicillin.⁴

The contributions to this symposium as well as the discussions were proof of the benefits derived from a close collaboration of clinicians with laboratory workers, and the conference as such served to further close contacts between the various groups of workers

² [see BMB 294] ³ [see BMB 199] ⁴ [see BMB 202]

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EFFECT OF VITAMIN-C DEFICIENCY ON EXPERIMENTAL WOUNDS

by G H. Bourne, *Lancet*, 1, 688-691, 27/5/44

This is the first quantitative study of the effects of graded vitamin-C deficiency on the healing of skin wounds. Bourne's results confirm and in some respects amplify those of Hunt (1941)

A week before operation, guinea-pigs were placed upon a scurvy-producing diet (Bourne 1942) with or without daily supplements of pure ascorbic acid ranging from 0.25 to 30 mg. A pair of standard wounds was inflicted on each animal by making a full thickness skin-incision, $\frac{1}{2}$ inch [about 1.2 cm.] long, on both sides of the vertebral column

about half way between the posterior border of the ribs and the pelvis. Animals of all groups were killed seven days after operation. Some of the scars were reserved for histological examination, and others were tested for the efficiency of wound healing by determinations of the tensile strength of the suture line—a technique introduced by Harvey (1929) and since then widely used. A rectangular slot of skin of standard width containing the suture-line was gripped firmly at both ends by toothed clips. One end was fixed to a vertical support and the other used as a balance pan, weights being attached to it until the suture line ruptured. Estimates of the tensile strength were very variable, both between different animals and between the wounds on either side of any one animal. The variation was not, however, large enough to mask the increase in wound strength with increased daily supplements of vitamin C. The mean tensile strength in grams for wounds in animals receiving no daily supplement was 25.3 ± 7.4 , with a daily supplement of 0.5 mg daily, 118.5 ± 18.0 , and of 2 mg daily, 338.7 ± 26.8 . Higher daily supplements were not found to raise the tensile strength further.

The histological appearances were very variable in general, more reticulin fibres were found in wounds with low tensile strength, but the author points out that the tensile strength of a wound cannot be guessed reliably from its histological appearance.

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A STUDY OF EPITHELIAL REGENERATION IN THE LIVING EYE

by I. Mann, *British Journal of Ophthalmology*, **28**, 26–40, January 1944.

The healing of wounds of the cornea may be watched by naked eye in any species which has pigment-granules in the basal-layer cells of the epithelium of the "limbus," i.e. the ring of contact between corneal and conjunctival epithelium. Rectangular defects in the corneal epithelium alone, 2.5 mm. inwards from the limbus, are repaired by the visible "creep" or "slide" of the pigment-bearing cells towards the centre of the corneal surface. Pigmented epithelium which has been caused to grow thus far inwards may be made to move even farther by making a second corneal defect nearer the centre than the first, this time about 5 mm. from the limbus. But if the first incision was made 5 mm. inwards from the limbus, there is no displacement of the pigment-bearing cells: the defect is repaired by the unpigmented epithelium of the corneal surface itself, a process not visible to the naked eye.

Just the same process was found to occur when the underlying substantia propria was destroyed by the action of various chemicals. The epithelium heals within a few days by "sliding," although pathological changes in the tissue which underlies it may persist for weeks. Arsenical war gases, by contrast with other chemicals, cause a proliferation of the pigment-bearing cells. This begins only after epithelial sliding has come to an end, and is quite distinct from it. Equally distinct is the isolated outward migration of pigmented cells from limbus to conjunctiva in cases of vitamin-A deficiency, a process not necessarily preceded by epithelial loss.

Professor Mann's paper confirms what is known of the healing of corneal defects in particular and epithelial wounds in general.¹

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PHOSPHATASE AND THE REPAIR OF FRACTURES

by G. Blum, *Lancet*, **2**, 75–78, 15/7/44.

It was found that the reunion and sound healing of experimentally-produced defects in bone could be accelerated by introducing bone- and kidney-phosphatase in a suitable vehicle between the divided stumps. The object of the vehicle was to prevent the loss of enzyme by oozing and

diffusion, not to provide a medium for cell growth. Not all vehicles were equally suitable, for *in vitro* tests showed that phenol-formaldehyde abolished the action of the enzyme, and that cellulose acetate greatly reduced it.

The vehicle eventually chosen was a 5% solution of sodium alginate clotted by the addition of calcium chloride. Phosphatase and its substrate, calcium glycerophosphate, were mixed with it and introduced into a 3–5 mm. defect cut in the radius bone of the rabbit. The healing process was watched by radiography and checked histologically. Healing was found to be more rapid in the phosphatase-treated fractures. That the enzyme preparation does stimulate or make possible the new formation of bone was confirmed by injecting the mixture into muscle. Ectopic bone in due course developed. In control experiments, the vehicle itself was found to be without effect.

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EXPERIMENTAL OBSERVATIONS OF THE USE OF ABSORBABLE AND NON-ABSORBABLE PLASTICS IN BONE SURGERY

by G. Blum, *Proceedings of the Royal Society of Medicine*, **38**, 169–171, February 1945.

For the purpose of this investigation non-protein and protein plastics were used.

The protein plastics were made from casein, fibrin, casein with plasma, erythrocytes and whole blood. Casein plastic was chiefly studied. Unlike the non-protein plastics, the protein plastics (which were formalized) are absorbable in animal tissues. They can be machined to provide screws, plates, blocks and triffin nails. Their strength, which is comparable to that of bone, increases with the degree of formalization. Their speed of absorption in the tissues depends on the degree of formalization, the bulk of the implant and the tissue at the site. A protein plastic implanted in tissue becomes at first rubbery, later soft and granular, then liquefies and finally completely disappears. The fibrous reaction which occurs during this process is greatly diminished after the plastic has disappeared. Bone implants of protein plastic are replaced by newly-formed bone. Softening and liquefaction are partly due to the action of proteolytic enzymes which break down the casein or fibrin of the plastic into peptones or polypeptides. No evidence of allergy has been found in animal experiments. These plastics are sterilized by autoclaving for 20 minutes at 120° C.

Non-protein plastics studied included methyl methacrylate (Perspex), cellulose acetate, nylon, urea formaldehyde and phenol formaldehyde. Methyl methacrylate alone proved sufficiently satisfactory for surgical application. Methyl methacrylate plastic is stronger than casein plastic. It has no advantages over metals, but the disadvantage of being a much weaker material. Methyl methacrylate is used in dental, facio-maxillary and cranial surgery.

The author refers to two methods for shortening the procedure when methyl methacrylate is used. In the first, unplasticized methyl methacrylate is used. This becomes easily mouldable on heating to 130° C., and sets on rapid cooling. Subsequent autoclaving or boiling do not cause loss of shape. Completed prostheses have been obtained in 15 minutes by this method.

In the second method, methyl-methacrylate dough containing a special catalyst is used. This undergoes hardening and polymerization when exposed to ultra-violet rays for 20 minutes at temperatures not above that of the body.

A fuller report of this work will be published in the *Lancet*.

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CANCELLOUS CHIP GRAFTS FOR THE RESTORATION OF BONE DEFECTS

by A. R. Mowlem, *Proceedings of the Royal Society of Medicine*, **38**, 171–174, February 1945.

Some modern methods of grafting owe more to carpentry than to the consideration of biological requirements, as the material chosen as the graft has been selected for its stability and not for its viability. More stress should be placed on viability than on stability, if bone is to be transplanted which will survive from the time of its insertion. In this respect cancellous bone possesses characteristics differing from those

¹ [see BMB 684 in this number —Ed.]

of cortical transplants. It rapidly undergoes the changes necessary to suit it to its new location and is unusually resistant to infection. These characteristics depend upon an adequate vascular supply.

The author believes that this type of bone survives transplantation and retains its cellular activity, because it is an open network of bony tissue containing many bone cells within easy reach of their new blood-supply. Full advantage is taken of this by fragmentation, which increases the surface-area.

The author has used chips of cancellous tissue from the iliac crest in over 80 cases. To restore continuity of the facial or cranial bones, chips are built up to the desired shape and kept in position by light bandage-pressure maintained for 5-7 days. In 35 cases of mandibular loss, clinical rigidity and the discontinuance of splintage have been obtained in 26 days.

In restoring continuity, skeletal pin-fixation or plaster casts have so far been sufficient, but in some cases internal splintage with cortical bone or by plating may be desirable. Once stability is obtained, all eburnated bone is removed and as much scar-tissue as possible is excised from between the bone ends. The requisite bulk of shaft is then built up by cancellous chips, which are fixed by suture of the soft tissues over them.

Cases of compound fracture of the tibia with skin- and bone-loss of long duration, and with grossly insufficient vascularity, have been successfully treated. One such case with a 1-inch [about 2.54 cm] tibial defect was walking without splintage in 10 weeks.

In 11 instances, grafts have been inserted in areas known to be infected. In one case of extensive jaw-defect with residual osteomyelitis, the area of infected bone was excised, a fistula with the mouth sutured, the defect grafted by chips, and a penicillin tube inserted. The graft was satisfactory. A case of tibial defects infected with *Ps. pyocyanea* was successfully treated, and the good result in this case was not due to penicillin as this particular organism is resistant.

It is not suggested that it is desirable to insert a bone-graft in the presence of infection, but it seems probable that a low grade localized infection need not be a barrier to bone-grafting which, if carried out before irremediable atrophy occurs, will effect a closer approximation of the resultant limb to normal.

The adoption of a biological standard implies the choice of a less rigid and more cellular type of bone than is usually employed, and something other than the graft itself is required for the provision of immediate stability of the bone ends. The creation and conservation of blood-supply is essential, even if this involves abandoning wide subperiosteal exposures and beautifully carpentered joints. The resultant technique can be applied earlier, with more certainty and much more rapid results than have hitherto been obtained.

with nembutal (15 mg/kg) by immersing the fore- and hind-limbs in water at 86° C for 2½ minutes. This treatment produced burns involving about 20% of the total body-surface and extending about midway through the dermis. This amount of injury is near the lethal border-line.

An uncomplicated and untreated thermal burn runs a constant course in the goat which is similar to the course in man. Within ½-hour of burning, much plasma leaves the vessels in the affected region. This results during the first 4 hours in a rapidly increasing haemoconcentration (increase in haemoglobin by $33.17 \pm 3.71\%$), a fall in plasma volume by $31.33 \pm 3.03\%$, and a decline in the serum-protein concentration by $20.0 \pm 1.71\%$. Eight to nine hours after burning a gradual recovery sets in, and at 24 hours haemoglobin, haematocrit and erythrocyte count are normal, but plasma volume is still slightly below normal. The serum proteins recover only after 3 days. Local oedema at the burn site increases during the first 24 hours but subsides afterwards. In the "pressure-treatment" of burns quick-setting plaster bandages were applied tightly to the burnt extremities so as to raise the subcutaneous-tissue pressure by 5-7 mm of Hg. The plaster bandages had to be applied with a considerable overlap beyond the burn margins, as oedema fluid tended to be squeezed some distance from the burn by the bandages. When the pressure was applied immediately after burning, the degree of haemoconcentration and the fall in plasma volume was only one-third, and the fall in serum-protein concentration only one-half of that observed in untreated animals and recovery set in much earlier than in the untreated controls. A delay of 4-6 hours in the application of the pressure-bandages diminished the value of the treatment. Skin-tight bandages not raising the subcutaneous tissue pressure, though useful, gave inferior results to those obtained when pressure was applied. In the authors' view, the beneficial effects of the pressure-bandages can be explained most simply by the assumption that the increased tissue-pressure combats the increased capillary permeability in the burnt area, thus preventing local plasma loss and lessening the main danger during the first stages after burning. The results presented support the favourable opinion expressed towards the "pressure-treatment" of burns by an increasing number of observers, whose work was reviewed by Rossiter (1943), Rossiter & Peters (1944), and Glenn, Gilbert & Drinker (1943).

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[BMB 702]

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PLASMA LOSS IN BURNS

by R. J. Rossiter, *Bulletin of War Medicine*, 4, 181-189, December 1943.

This is a very useful review of literature up to the end of 1943, prepared by one of the workers of the department of biochemistry, Oxford, for the Burns Sub-committee of the War Wounds Committee of the Medical Research Council. The following is the author's summary.

i The evidence that there is a loss of fluid from the bloodstream to a burned area is reviewed. This evidence includes the direct measurement of the fluid accumulating at the site of the burn, observations on the haemoconcentration and on the plasma volume. In animals, burned experimentally, there is little external fluid loss, but this may be greater in human burns. There is little evidence for a loss of fluid to parts of the body other than those directly involved in the burn.

ii A direct chemical analysis of the burn exudate, and of the lymph drained from the burned area, indicates that, as well as loss of fluid, there is a loss of protein. This loss causes a decrease of the plasma proteins, but measurements of the latter reveal that the decrease is not as great as would be predicted. This is possibly due to the rapid mobilization of readily available protein reserves. In experimental animals, there is little external loss of protein, but this may be of greater significance in man.

iii Shock is one of the most obvious clinical manifestations of severe burns. Evidence is given for the view that

Burns and their Treatment

The articles by Prof. R. A. Peters (BMB 688), Prof. G. R. Cameron (BMB 689) and Dr. F. H. K. Green (BMB 690) cover the subject of this section so comprehensively that the only other papers reviewed are those which deal with a particular aspect of burns or which give statistical information on large numbers of cases.

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A STUDY OF THE EFFECTS OF APPLYING PRESSURE TO EXPERIMENTAL THERMAL BURNS

by G. R. Cameron, J. W. Allen, R. F. G. Coles & J. P. Rutland, *Journal of Pathology and Bacteriology*, 57, 37-46, January 1945.

In this article, which is the authors' report to the Burns Sub-committee of the Medical Research Council's War Wounds Committee, experiments are recorded which were designed to assess the value during the first 24 hours of the prompt application of pressure to experimentally burnt limbs and to clarify our knowledge of the principles involved in such treatment. The burns were produced in goats anaesthetized

the plasma loss known to occur after severe burning is, in most cases, sufficient to initiate burn shock

iv Other possible causes of shock—nervous stimuli, toxins from damaged tissue, bacterial toxins, high blood-potassium, etc.—are briefly considered

v The normal mechanism of fluid exchange between the capillaries and tissue fluid is given, together with a discussion of the disarrangement of this mechanism when the tissues are damaged by burning

vi It is suggested that the following measures might be taken to diminish oedema formation

- a Decreasing capillary hydrostatic pressure by elevation of the injured part (gravity effect)
- b Increasing colloid osmotic pressure by plasma or serum infusions
- c Decreasing capillary permeability by oxygen therapy, adrenal cortex hormone treatment, and ensuring that the skin of the burned area is kept at a temperature of 70–80° F [about 21–27° C]
- d Increasing the tissue pressure by skin-tight plasters, pressure dressings or some other device
- e Promoting lymph flow from the injured part by elevation (gravity effect)

Of these suggestions, *b* is generally employed by surgeons in Great Britain at the present time, *a* and *e* are used by some, *c* is still in the experimental stage and more clinical observations would be of value, while *d* is relatively new. It is stressed that, because of the extreme rapidity of the fluid loss, these measures should be instituted as soon as possible after the burning, and that they should not be delayed until the clinical signs of shock develop

In a paper that has appeared since the preparation of this survey, Glenn, Gilbert & Drinker (1943) stress some of the arguments developed here. They also make the important point that coagulation of the plasma exuded in and about the burned area not only results in a mass of abnormal material which must be removed during healing and provides a culture medium for bacterial growth, but predisposes to subsequent deformity through an excessive formation of fibrous tissue. The conclusion of Barnes & Trueta (1941), that the application of a skin-tight plaster to a burned limb diminishes both local swelling and lymph flow, has been confirmed

Many of the suggestions presented here arose from numerous discussions of the problem with Professor R. A. Peters, F.R.S., and others arose from an informal meeting called to discuss a memorandum from Dr R. B. Bourdillon to the Burns Sub-committee (Bourdillon, 1943)

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THE DIAGNOSIS OF THE DEPTH OF SKIN DESTRUCTION IN BURNS AND ITS BEARING ON TREATMENT

by D. H. Patey & R. W. Scarff, *British Journal of Surgery*, 32, 32–35, July 1944

The authors, in view of the difficulty of assessing the depth of skin destruction in burns by clinical observation alone, have investigated other ancillary methods. They first examined microscopically portions of the skin separated by blistering. Two main planes of epithelial separation were found through the stratum granulosum, and through the stratum malpighii. No evidence of the traditional plane of separation leaving interpapillary epithelial columns intact was seen. Even complete epithelial loss, down to and including the stratum malpighii, was compatible with rapid primary re-epithelialization from hair-follicles and glands in the dermis, provided that the dermis was not involved in the original coagulation-necrosis from the burn, and did not become damaged by subsequent septic infection.

The authors refer to cases in which histological observations corrected wrong clinical impressions on the depth of epithelial destruction. The disadvantages of the histological method are the time that must elapse before the microscopical sections are prepared, and the fact that, if blister-epithelium only is examined, no information is given of the condition

of the underlying dermis. The authors therefore endeavoured to find a rapid method for the diagnosis of coagulation necrosis of the dermis. In their tests they burnt the skin of breasts immediately before operation for radical removal, noting the depth of dermal necrosis by subsequent whole thickness microscopical sections.

In the microscopical sections Werlhoff's elastic stain was found useful for identifying dermal necrosis, but the most useful stain for clinical use was van Gieson's (picro-fuchsin). This is normally bright red in colour but, if applied to an area of necrosis, a yellowish tinge appears, which becomes more marked as the necrosis is more marked. The authors suggest that, if by some such staining method as this dermal necrosis could be recognized in the acute phase of a burn, primary débridement¹ and skin-grafting might be carried out.

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TREATMENT OF BURNS WITH PARTIAL SKIN DESTRUCTION: AN ILLUSTRATIVE CASE

by D. H. Patey & R. W. Scarff, *Lancet*, 1, 146, 3/2/45

The authors describe a case of burns in which they used van Gieson's stain to determine the amount of dermal necrosis.² The progress of the case showed that the original assessment of dermal necrosis was a correct one. The case was a burn of the buttock, with superficial necrosis only of the dermis and preservation of almost all the follicular epithelial islets. In spite of this, re-epithelialization took six weeks, largely owing to the time necessary for the separation of the dermal sloughs. The authors suggest that quicker healing would probably have occurred if a primary excision of the dermis had taken place, followed by skin-grafting, in other words, that the essential criterion in deciding to treat a burn by primary débridement¹ and skin-grafting should be not so much that the follicular epithelial islets have been preserved but rather that substantial dermal necrosis, which will take a long time to separate, is present.

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BURNS AND SCALDS IN CHILDREN: AN INVESTIGATION OF THEIR CAUSE AND FIRST-AID TREATMENT

by A. W. Wilkinson, *British Medical Journal*, 1, 37–40, 8/1/44

The author contends that there was an increase in the incidence of burns and scalds in Edinburgh district during the past 3½ years. It is difficult to see the basis for this, because if "incidence" denotes, as it should, the ratio of the number of cases to the population, then no evidence of the increase is offered.

All that is shown is that in the last 2 months of 1939 and the first 2 months of 1940, the number of cases was twice as great as in the corresponding periods of the 5 previous years (Table II in the original paper). But at one dispensary the proportion of burns and scalds in children to the total out-patients (Table V in the original paper) showed a decline for 1940–43 compared with 1936–39. The increase in cases might well be related to movement of the population during the early years of the war. Later it is stated that the greatest incidence (number of cases) was in those areas where the population is most dense. Naturally, where there are more people there will be more cases. Here again the numbers should have been related to the population of the areas.

The report, however, provides an interesting statistical analysis of 366 children under 12 years of age admitted to the

¹ [This word is widely used in English-language surgical literature to describe excision of wound-edges and necrotic tissue—without reference to the release of tension. Some surgeons, however, prefer to restrict its use to its original sense of division of constricting bands—or, by extension—to the relief by cutting of tension or constriction due to other causes.]

The employment of *débridement* in the wider—and etymologically incorrect—sense is presumably due to the mistaken supposition that it is derived from *débris*, and therefore implies the removal of dead or damaged tissue from a wound. It is in fact derived from *bride*, and implies the removing of a bridle. It is surely unfortunate that the same word should be used in totally different senses in English-language and French-language surgical literature.—Ed.]

² [see BMB 703—Ed.]

Royal Hospital for Sick Children, Edinburgh, between June 1st 1938 and July 31st 1942. Scalds accounted for 81% (298), and the remainder were admitted for burns.

The predominance of males (211 to 155 females) is accounted for, rather surprisingly, by their preponderance in one age-group (136 males to 76 females between 1 and 3 years). A very high proportion of the children (40%) was between 1 and 2 years of age. Only 12% were in the 5-12 years group.

The burns can be subdivided by cause into three main groups: clothing 20, fireplaces 25, others 13. Scalds were caused in 91 instances by cups of tea, 63 by saucepans, 59 by kettles, 43 by teapots, 20 fell into hot-water containers, leaving a miscellaneous group of 22. The fatality-rate in burns was 10.3%, in scalds 3.7%, a statistically significant difference.

The time of occurrence was known in 132 cases, and there seems no obvious reason why this should not be a random sample. The relation between time and age is not shown, but considering all ages combined, the peak was between 5.0 and 7.30 P.M. Few instances occurred in the morning but an unduly large number between 9.0 and 11.0 P.M.

Fatality was high in the 1st, 4th and 5th years of life. Between 11% died in these age-groups as against 2% in the 2nd and 3rd years of life, and 2.2% [misprinted as 22% in the original] in the age-group 5-12.

The extent of the injury is of course the important factor as regards fatality-rates, which varied from 19% to 3%, according to whether the area burned was greater or less than 15% of the body-surface.

From the fact that 88% of the deaths in this series occurred at ages under 5, and that the proportion is almost the same as in comparable series relating to the years 1899-1903, and 1924-28, the author concludes that the limit to which fatality can be reduced has been reached. Measures to reduce the actual number of incidents are the urgent present-day need and, in propaganda to meet this, education as to proper first aid treatment should play an important part, as analysis showed that, in the great majority of the cases, first-aid treatment had either been badly done or was of an undesirable nature.

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SOME SOCIAL ASPECTS OF BURNS IN GLASGOW

by A. Brown, E. Lewis-Fanning & M. M. Whittet, *British Medical Journal*, 1, 144-146, 3/2/45

This report is supplementary to *Studies in burns and scalds* (Medical Research Council, 1944) and is primarily a statistical analysis of 1803 patients of all ages, treated in the burns unit of the Glasgow Royal Infirmary between January 1942 and August 1943. Of this total, 303 (16.8%) were admitted as in-patients.

From a comparison between the age- and sex-distribution of the patients and that of the 1931 Census population for Glasgow, the authors deduce (a) that burns are more frequent among males than females at every period of life (ratio 128:100), (b) that the highest incidence occurs at the youngest ages (25% occurred in the first 3 years of life), but (c) that the injuries are more serious in older patients (59% of the in-patients were over 51 years of age).

Industrial accidents accounted for 17% of the 303 admissions, domestic accidents 83% (and of the latter, 53% were scalds and 43% due to fire).

The relation between time of burning and age was examined in detail. Whilst 2.0 P.M. to 8.0 P.M. was found to be the period of greatest frequency, yet about one-fifth of the total burns (386) occurred between 8.0 P.M. and midnight. Of these, 287 (74%) were sustained by children under 16, and 144 (37%) by those under 4. "It is a grave reflection that from 8 P.M. to midnight—i.e. a time when one would expect young children to be in bed and safe—three-quarters of the burns sustained occurred at these young ages."

An analysis of the extent of the burned area in patients admitted to hospital led to the conclusion that burns were on the average more serious amongst females, and fatality-rates support this view.

REFERENCE

¹ Medical Research Council (1944) *Spec. Rep. Ser. med. Res. Coun., Lond.* No 249

² [BMJ 719/127]

BURNS AND THEIR TREATMENT AMONG E.M.S. HOSPITAL IN-PATIENTS

by E. M. Brooke, *British Medical Journal*, 1, 259-260, 24/2/45

A random sample of 400 burned patients (355 males and 45 females) admitted to Emergency Medical Service hospitals from the Armed Forces during 1943 and the first half of 1944 is analysed statistically.

As would be expected from the source of these data, the age distributions show a concentration around 15 to 35 years. Forty-one per cent of the males (145) were under 25, and 44% (156) between 25 and 35 years of age. Sixty-two per cent of the females (28) were under 25 and 31% (14) in the 25-35 age-group.

Analysis by site of burn is complicated by the fact that in 27% there were multiple sites. Excluding these, the hands and lower limbs were sites of greatest frequency. Face, head or neck appeared in 37% of the records.

The cause of the burn in 170 instances (42%) was fire and hot objects. In many cases these were due to avoidable accidents: burning petrol, flames from fires, blow-lamps, cookers, etc. Only 23 of these were due to incendiary bombs and other instruments of war. Forty-three of the total burns (10.75%) were due to phosphorus. No doubt the group of 103 (about 25%) labelled "other and unqualified" cause, were due to a large number of varied agents, each accounting for but a few burns, so that subdivision was unwarranted. For 40% of the patients, no record was available as to whether the burn was of the 1st, 2nd, or 3rd degree. This deficiency in the data is perhaps not surprising but certainly detracts from the value of the threefold analysis by site, degree and length of treatment with which the author concludes her paper.

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BURNS OF THE HAND

by P. H. Jayes, *British Journal of Industrial Medicine*, 1, 106-109, April 1944

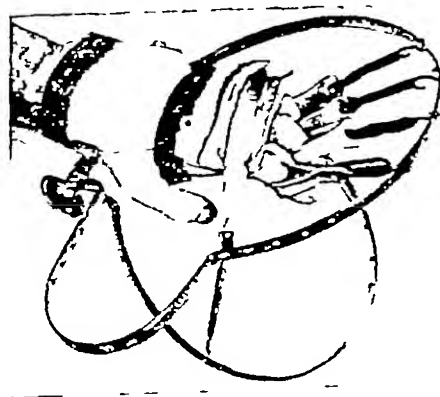
The author emphasizes the importance of burns of the hand in industrial medicine. Under normal civilian conditions no elaborate first-aid treatment is indicated, but the patient should be admitted as soon as possible to hospital. In hospital, the burned hands are thoroughly cleaned with "cetavlon," blistered skin is cut away, and the fingers are dressed individually with paraffined gauze. The initial dressings are changed after 3-4 days, and subsequently twice daily, by soaking in saline. Oedema is treated by elevation and the hand is splinted in the position of function. After the oedema has subsided, which should happen in a few days, the splints are removed and active movements are started. In cases with whole-thickness skin destruction, skin-grafting is performed as soon as sloughs are separated. Two cases are illustrated, treated by skin grafts cut by a Padgett dermatome.

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FINGER EXERCISER FOR BURNED HANDS

by M. C. Oldfield & C. J. King, *Lancet*, 2, 109, 22/7/44

The authors describe the use of a finger exerciser in the treatment of burned hands. It consists of an aluminium splint strapped to the wrist with two loops attached, from



which rubber bands can exercise elastic traction. The splint is used to combat contractions, exercise weak muscles and stretch shortened ligaments. Three months' experience with the splint in a facio-maxillary unit in the Middle East proved its value.

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DISCUSSION ON BURNS OF THE EYELIDS AND CONJUNCTIVA

by C P G Wakeley, D C Bodenham, F Ridley & G W Cashell, *Proceedings of the Royal Society of Medicine*, 37, 29-34, November 1943

Surgeon Rear-Admiral C P G Wakeley, speaking of his experiences in the Navy, stressed that in the first World War it was realized by 1916 that the two outstanding desiderata in the treatment of burns were elimination of sepsis, and skin-grafting of third-degree burns. The superficial burns, as also splitting of the skin from the blast of a bomb-flash, healed well, especially when they affected the face with its richly vascularized skin. Sulphonamide ointments, such as sulphathiazole cream, do much to combat sepsis, though in the deep burn there is a potential danger of sulphonamide-poisoning from massive absorption. Triple-dye or gentian violet gives good results. Intravenous plasma or saline are rarely necessary. The loss of fluid can usually be countered by the free administration of fluids by mouth.

Like Mr Wakeley, Flight-Lieutenant D C Bodenham stressed the danger of the use of tannic acid. If infection develops it should be treated specifically. Early healing should be the aim, assisted by skin-grafting where necessary.

The need for preventing symblepharon by the use of rapidly-made plastic lenses was discussed by Squadron-Leader G W Cashell, whilst Mr Frederick Ridley emphasized the necessity of protecting the cornea, which becomes exposed owing to damage of the lids. A device whereby a contact-lens can be mounted on to the cornea from an extension of a dental cap-splint had proved useful in cases in which a contact-lens could not be retained otherwise.

The view that the liver-damage often found in cases of fatal burns may be due to treatment with tannic acid received much support from many clinical reports. In several series of cases it was shown that this lesion was absent from patients dying from burns, who had not received tannic-acid treatment, but it was present in 60 % of those who had been thus treated. Moreover it appeared that, although in untreated cases the main mortality occurred during the period of primary shock (12-36 hours), in cases treated with tannic acid the main mortality occurred during the later period of toxæmia (3-6 days), which is the time when the necrotic lesion in the liver is most often found. In view of all these facts it became clear that there was need for careful investigation of the whole question of the toxicity of tannic acid and its relation to the hepatic damage noted. The three papers reviewed below describe the results of such investigations by experimental methods in animals.

Cameron, professor of morbid anatomy in the University of London, and his colleagues Milton and Allen found that guinea-pigs and goats were the animals most susceptible to injections of tannic acid, and rabbits and rats the least susceptible. After doses which caused death in a few days, the animals were noticeably quiet, taking much water but no food, and exhibiting severe wasting and diarrhoea. The liver was swollen, with areas of yellow or grey necrosis, while the kidneys were swollen and pale. Microscopically, there was severe damage to the liver-cells, beginning as coagulation-necrosis of the centre of the lobules. This necrosis spread until most of the liver consisted of areas of necrotic cells rimmed by narrow zones of healthy or fat-containing liver-cells. If the animal did not die after 2-3 days, regeneration of the liver-cells gradually occurred. The renal changes were relatively slight and transient, including cloudy swelling of the convoluted-tubule cells and similar changes. If the tannic acid was injected subcutaneously, it caused, within 24 hours, extensive oedema around the site of injection. The permeability of the blood-capillaries in general was considerably increased, so that fluid leaked out of the circulation into the subcutaneous tissues, peritoneum and elsewhere, causing haemoconcentration and a diminution of the blood-volume, the concentration of the plasma-proteins also diminished, while that of the non-protein nitrogen in the blood increased. Leucocytosis also occurred.

In order to investigate the absorption of tannic acid and gallic acid from burnt surfaces, methods for estimating these two compounds in the blood were developed, the method for tannic acid consisted of measuring the depth of bluish-purple colour which develops when small amounts of ferric chloride are added to plasma, that for gallic acid depended upon the oxidation of gallic acid by hypochlorite in alkaline solution to a coloured quinonoid complex. By these means it was shown that when tannic acid is applied to large burns of animals (goats, rabbits and rats), tannic acid is found in the blood, and if large amounts are present liver-damage often occurs. The more extensive the raw vascular surface, the greater the risk of tannic-acid-intoxication will be. The injurious effects are not due to gallic acid, which is rapidly removed from the blood and which can be tolerated in large amounts.

Similar experiments were carried out by Barnes and Rossiter working in the departments of pathology and biochemistry at Oxford. They found that the toxicity of tannic acid for animals depended greatly on the method of administration. Thus 20 mg given intravenously killed a guinea-pig within a few minutes, while 1.6 g given intramuscularly failed to kill guinea-pigs within 24 hours. Burns were produced in anaesthetized guinea-pigs by applying a vessel containing water at 70-80° C to the clipped skin for half a minute, the burned area was denuded of epithelium by rubbing it with moist cotton wool, and tannic acid (20 % solution) was applied three times in the next 24 hours, a hard black scab formed. The burns were situated on the belly and occupied about a quarter of the body surface, larger burns were fatal within 24 hours. Animals treated with tannic acid had a higher mortality (4 died out of 18) than those left untreated (1 died out of 18) or those treated with normal saline (none died out of 12). Moreover, the animals treated with tannic acid lost much more weight than did the controls.

After the injection of large doses of tannic acid, it could be detected in the liver for 24-48 hours, and also in the lungs and kidney. When tannic acid was applied to a large burnt area, it could be subsequently detected in the liver, lungs and

Toxic Effects of Burn Treatment

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I. TOXICITY OF TANNIC ACID · an Experimental Investigation

by G R Cameron, R F Milton & J W Allen, *Lancet*, 2, 179-186, 14/8/43

II. TOXICITY OF TANNIC ACID

by J M Barnes & R J Rossiter, *Lancet*, 2, 218-222, 21/8/43

The treatment of burns by the local application of solutions of tannic acid was introduced by Davidson in 1925, and was based on two conceptions. In the first place it was believed that it prevented the absorption of toxic substances from the burnt area, because these were precipitated as insoluble tannates. In the second place, it prevented excessive loss of plasma and other fluids by covering the raw area with a firm coagulum. The new treatment was quickly hailed as a great advance, and the death-rate from burns in almost all the published figures fell rapidly. Part of this improvement must be attributed to the improved treatment of shock and of dehydration, but much of it seemed clearly to be due to the tannic-acid treatment.

With the onset of the present war, burns became of great importance, forming one of the major groups of casualties. At first tannic acid was universally employed, but gradually its use came to be regarded with doubt. In burns of the hands and face it caused late contracture, and its employment was abandoned. The work of Wilson, MacGregor & Stewart in Scotland in 1938 had called attention to severe necrotic damage to the liver in fatal burns, and had aroused the suspicion that this lesion might be due to the toxicity of tannic acid, as this substance would produce similar lesions in animals. This suspicion was greatly strengthened by Wilson's work with the armies of the Middle East and by similar observations reported by Wells, Humphrey & Coll (1942).

kidney, and also in the muscles lying below the burnt area. The histological changes in the liver were the same as those described by Cameron and his associates, i.e. those of necrosis. In a supplementary report, Clark & Rossiter (1943) show that the subcutaneous injection of tannic acid into rabbits causes functional changes in the liver as well as histological changes, as performance in the galactose-tolerance test is depressed.

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LIVER FUNCTION AFTER BURNS IN CHILDHOOD CHANGES IN LAEVULOSE TOLERANCE

by S. L. Rae & A. W. Wilkinson, *Lancet*, 1, 332-334, 11/3/44

Experience gained in Britain and America shows that treatment of burns, especially if these are extensive, with tannic acid may lead to severe toxæmia and liver necrosis. It is for this reason that W. C. Wilson in 1938 started using 10% silver-nitrate solution instead of tannic acid at the Royal Hospital for Sick Children, Edinburgh. The authors of the present article, at the same hospital, investigated the liver function by the laevulose-tolerance test in 27 children varying in age from 7 months to 11 years and suffering from burns and scalds. In twelve of these, with 5-45% of the body surface affected, the burns were treated by coagulation with 2% gentian violet followed by 10% silver-nitrate, in 7, with 5% of the body-surface burnt, with sulphacetamide paste, and in 8, 5% of the body-surface being burnt, with tannic-acid jelly containing 5% tannic acid and 1 part in 5,000 of "merthiolate".

Impairment of liver function, which was found mostly between the 3rd and 6th day after burns, was least in patients treated with gentian violet and silver nitrate (despite the more extensive burns in these cases), and was more common and most severe after treatment with the tannic-acid jelly, sulphacetamide occupied an intermediate position. The authors concluded that there is now sufficient evidence, both clinical and experimental, to justify disuse of tannic acid as a local application to burns. However, coagulation treatment has many advantages and may be life-saving in the early stages of very extensive superficial burns, and for this purpose silver nitrate is probably a safe coagulant. The authors utter a caution against the use of sulphonamides on large burns, as these drugs may be rapidly absorbed from the surface with consequent toxic blood-concentrations and sometimes liver damage.

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TOXIC EFFECTS OF PROPAMIDINE, WITH SPECIAL REFERENCE TO THE TREATMENT OF BURNS

by J. W. Allen, F. Burgess & G. R. Cameron, *Journal of Pathology and Bacteriology*, 56, 217-223, April 1944

At the request of the Burns Sub-committee of the Medical Research Council's War Wounds Committee, the authors investigated in the goat, rabbit, guinea-pig, rat and mouse the toxicity of propamide (4,4'-diamidino-diphenoxyp propane), a substance with bacteriostatic properties of value in the treatment of burns.¹ The lethal doses (LD₅₀) of propamide dihydrochloride, as mg./kg., were intravenously, for the goat 10, and for the rabbit 20, subcutaneously, for the rabbit 15, for the guinea-pig 10, for the rat 70, and for the mouse 40. Toxic doses, whether injected intravenously or subcutaneously, produced within 24 hours in all 5 species severe liver damage, ranging from hydropic and fatty degeneration to widespread necrosis of the liver cells. These changes may persist for 2-3 weeks, but usually healing is complete in about 8 days. In fatal cases, granular and fatty casts may occur in the convoluted tubules and Henle's loops of the kidney, but necrosis has not been found. Pulmonary

oedema was the immediate cause of death in about 12% of animals. Local reactions which develop at the site of subcutaneous injection in a few days include oedema, haemorrhage and muscle necrosis, these often progress to chronic inflammation.

When propamide in water-soluble-jelly base was rubbed into the shaved skin of rabbits or guinea-pigs, neither systemic toxic effects nor pathological changes in the organs were found.

To test whether propamide is absorbed from burnt areas, thermal burns involving about $\frac{1}{4}$ of the body surface and extending into the dermis for about $\frac{1}{4}$ - $\frac{1}{2}$ the distance between the epidermis and the underlying muscle were produced in rabbits. These burns were treated with 10 g. of propamide dihydrochloride ointment (0.1% propamide dihydrochloride) after the removal of dead skin, 4 applications having been made at 2-day intervals. After 9 days, 1 out of 6 rabbits showed extensive liver necrosis, the others showed no pathological changes. The dosage used was considerably in excess of what is likely to be used in man. In 10 guinea-pigs with extensive thermal burns, $\frac{1}{2}$ of the body surface being involved, treatment at 2-day intervals with 5 g. of propamide ointment led to no pathological changes in the organs.

Propamide isethionate is slightly less toxic than propamide dihydrochloride, but the pathological changes produced by toxic doses of the former were the same as those caused by the latter. No ill effects were observed after the application of propamide isethionate ointment (0.1% propamide isethionate) to either the normal or burnt skin of rabbits. The authors conclude that, although propamide dihydrochloride and isethionate are toxic in quite small doses when they reach the blood stream, propamide ointments may be applied to normal and burnt skin areas with little risk of absorption. Toxic effects are seen only after the use of considerable amounts of these ointments.

Experimental Shock

This subject has been well covered in articles by Prof. H. N. Green (BMB 692), Dr J. McMichael (BMB 693) and Dr E. G. L. Bywaters (BMB 694). The five papers reviewed here amplify or supplement the information given by them.

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EXPERIMENTAL TRAUMATIC "SHOCK"—FACTORS AFFECTING MORTALITY AND EFFECT OF THERAPEUTIC AGENTS (ASCORBIC ACID AND NUPERCALINE)

by G. Ungar, *Lancet*, 1, 421-424, 3/4/43

While surgical shock at present defies definition, it may reasonably be accepted as a grave condition occurring after injury, in the absence of haemorrhage, sepsis or injury to vital organs. It has been maintained that it is an "all or none" reaction, largely independent of the severity of the injury, but the author of this paper, like Noble & Collip (1942), has attempted to show that the severity of injury determines the degree of shock. Working with groups of small animals he accepts the death rate within the group as evidence of the degree of shock. The author, who is a member of the French Scientific Mission in Britain, collaborated with Dr S. Zuckerman at Oxford in investigating the effect of projectiles and blast on the animal body.

Technique. Adult guinea-pigs, rats and mice under urethane anaesthesia were used. The injury was produced by dropping a metal rod 12 mm. (for guinea-pigs) or 6 mm. (for mice) in diameter through a vertical tube on to the adductor region of the thigh. The severity of the injury was varied by varying (a) the height from which the rod was dropped, and (b) the number of times it was dropped. The relative severity of the injury was expressed in kg. m., that is, as weight of rod multiplied by length of drop (or by the sum of several drops when more than one was used). The rod always caused an open wound and severe crushing of the muscles and occasionally fracture of the femur. After the injury the animals were watched for 10 hours under continuous anaesthesia. The conditions of the experiment excluded sepsis and injury to

¹ [see BMB 58—Ed.]

vital organs as causes of death, and animals in which there was much bleeding were discarded

I Relation between Severity of Trauma and Death Rate

Statistical analysis of the results in groups of 47 guinea-pigs, 81 mice and 20 rats showed that the death rate rose in direct proportion to the amount of the force producing the injury

II Factors influencing the Death Rate

In these experiments a constant force was used, being that which had been shown in the earlier experiments to be just sufficient to kill 100% of the animals

i *Seasonal variation* (guinea-pigs) There was a regular variation in death rate between summer and winter, the death rate in August being less than half that in December and January. The author is satisfied that the difference was due to changes in the animals and not to differences in the experimental conditions

ii *Previous trauma* (guinea-pigs) A small injury was given at an interval of from 3 hours to 3 days before the severe (standard) injury. This preliminary injury lowered the death rate, the decrease being greatest when the first injury preceded the second by from 2 to 3 days. Serum taken at this time from guinea-pigs which had been slightly injured, and injected into guinea-pigs or rabbits at the time of a severe injury, lowered the death rate in these animals also. The smallest doses given, 0.1 cm³ per kg to guinea-pigs and 0.01 cm³ per kg to rabbits, were effective

iii *Ascorbic acid* A dose of from 100 to 500 mg per kg given to guinea-pigs 15 minutes after the injury greatly lowered the death rate, but at 30 minutes the effect was less. The author believes that the effect is not due to its action as a vitamin. Holmes (1942), following the preliminary publication of this work, used ascorbic acid with good effect in human cases of shock

iv *Local anaesthetics* Certain Soviet surgeons, whose work is reviewed by Clarke (1941), systematically used the local anaesthetic sovkaïn (nupercaine) in war surgery, and reported a greatly decreased incidence of traumatic shock. In the present experiments the author injected 4 mg per kg of nupercaine at the site of trauma (as a 1/5,000 solution) or into a distant limb (as a 1/100 solution). Injection at either site was effective in reducing the death rate, from which it appears that the beneficial action of nupercaine does not depend on anaesthesia of the injured area. Another local anaesthetic, procaine, was without effect on the death rate

Throughout the work all animals were examined *post mortem*. In those which died early there was visceral hyperaemia, later there was haemorrhage and oedema in the thoracic and abdominal organs. Subendocardial haemorrhages were also seen. The author believes that the animals died from a condition analogous to surgical shock in man, and that any treatment which lowers the death rate under the conditions of these experiments is worth a clinical trial

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INTRACISTERNAL INJECTION OF POTASSIUM PHOSPHATE

by C B B Downman & C C Mackenzie, *Lancet*, 2, 471-473, 16/10/43

Stern (1942a, 1942b) has advocated the use of potassium phosphate in shock after trauma or haemorrhage and has claimed that injection into the cisterna magna has benefited both experimental animals and battle casualties suffering from shock, the blood-pressure, respiration and reactivity rapidly becoming normal. Potassium salts in small quantities excite and in larger doses depress nervous tissue. Several workers have found that intracisternal or intraventricular injections of potassium chloride cause a rise of carotid blood-pressure and adrenalin secretion with increased respiration and muscle tone. Ainslie & Dax (1942) found no significant rise of blood-pressure in 3 psychotic patients not suffering from haemorrhage or shock, whereas in 6 cases

there was a transient fall and a marked slowing of the heart followed by nystagmus and sweating. The present authors, of the Sherrington School of Physiology, St Thomas's Hospital, London, report experiments with adult rabbits anaesthetized with urethane or pentobarbital on the effect of intracisternal injection of potassium phosphate on blood pressure, respiration, and skeletal muscle tone. Blood pressure and heart- and respiration-rate were optically registered. The solutions used were (a) 1/6 molar potassium dihydrogen phosphate diluted with 1/6 molar potassium hydroxide to pH 7.6, (b) 1/6 molar phosphoric acid diluted with potassium hydroxide to pH 7.6 provided sterile in 1 ml ampoules

Carotid blood-pressure increased after a latent period of $\frac{1}{2}$ minute. This increase was usually slow and followed by slower fall to normal. The average duration was about 15 minutes, rarely lasting up to 45 minutes. The rise was often preceded by a sharp fall beginning 5 seconds after injection, and some animals failed to show any subsequent pressor effect. The depressor effect was accomplished by slowing of the heart-rate and was not modified by vagotomy. After a brief latent period respiration became quicker and deeper, increasing to a maximum in $\frac{1}{2}$ -2 minutes, but usually lasting as long as the blood-pressure change. With large doses, respiration might be inhibited for a few cycles. The tone of the voluntary muscles was increased, beginning in the shoulder muscles, where it was associated with slight tremor, and later spreading and producing head-retraction, strong extension of the limbs, and convulsions. These responses were decreased but not entirely abolished by section of the spinal cord between the 1st and 2nd cervical roots and of both vagus nerves. The responses were not altered by previous haemorrhage. The range of volume of phosphate solution injected was 0.01-0.05 ml. No permanent toxic effects followed the injection

The authors conclude that reactions were due to excitation of nervous centres above the spinal-cord level. Intravenous injection of such doses has no visible effect, nor does ten times the dose have any. The increased tone of the muscles probably accentuates any rise in blood-pressure, but Mullin, Hastings & Lees (1938) still obtained a rise after administration of curare in doses sufficient to paralyse voluntary muscles. The short duration and erratic responses following intracisternal injection of potassium phosphate do not, in the opinion of the authors, suggest that they would be of value in conditions of shock or of haemorrhage

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CAPILLARY PERMEABILITY IN TRAUMATIC SHOCK

by D Engel & E Forrai, *Journal of Physiology*, 102, 127-139, September 1943

The authors, working at the department of neurosurgery of the Royal Infirmary and the department of physiology of the Royal (Dick) Veterinary College, Edinburgh, investigated quantitatively the permeability of capillaries in traumatized limbs of cats and one rabbit by a method worked out by Engel (1940). This method consists essentially of the infusion of a 1% acid fuchsin solution into the jugular vein at the rate of 0.7 cm³ per minute, and the perfusion of both knee-joints with warm Ringer's solution at the rate of about 0.3 cm³ per minute. The dye is excreted through the knee-joint. The perfusion fluid of the knee-joints was collected half-hourly and, after the addition of a few drops of acetic acid to regenerate the colour of the dye, its fuchsin content was compared with a standard in a colorimeter and was expressed as mm of the height of column of the standard in the colorimeter. The experiments were performed under nembutal anaesthesia. The trauma consisted of 80-100 hammer blows to the soft parts of the extremities, but usually causing fracture of bones as well. When the hind-leg of cats was thus crushed below the knee, an increase in the excretion of the dye into the knee-joint commenced immediately after injury. The increased excretion lasted for 1-5

hours and at its maximum was 2-7 times that of normal. Three to five hours after the injury, the excretion of dye on the side of trauma decreased to about 50% of the normal. When the crushing was inflicted on the fore-legs there was no increase, but a decrease in the excretion of the dye through the synovial membrane of the knee-joint during the first 3-hour period after injury. This decrease was probably the result of a fall in the concentration of the dye in the blood, caused by a loss of dye into the crushed tissues of the fore-legs. When the infusion of the fuchsin solution and the perfusion of the knee-joints was started 23 hours after the crushing of one hind leg, when the animals were in a moribund condition and the crushed leg was very oedematous, the excretion of the dye through the knee-joint varied approximately between one-third and one-half of the normal.

The conclusion drawn from these results was that in traumatic shock an increased filtration through the capillaries occurs only in the area of injury and its immediate neighbourhood, and only during the first few hours after the trauma.

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RENAL DAMAGE DUE TO CRUSH INJURY AND ISCHAEMIA OF THE LIMBS OF THE ANAESTHETIZED DOG

by M. G. Eggleton, K. C. Richardson, H. O. Schild & F. R. Winton, *Quarterly Journal of Experimental Physiology*, 32, 89-106, 1943

The development of anuria in certain individuals who have suffered crushing injuries of the limbs has been described fully (e.g. Bywaters & Beall, 1941) and the associated renal lesion analysed in man (Bywaters & Dible, 1942). The experimental work of the present paper was designed to discover if prolonged crushing and ischaemia of the limbs in the dog would produce a rapid failure of renal function and throw light upon the mechanism of the lesion and the effect of therapeutic measures. The experiments were carried out under anaesthesia. The animals' hind legs were tightly bound from ankle to thigh with rubber tubing. Each thigh was then crushed in a vice for about five minutes and the muscles further traumatized by hammering. The bandages were left in position for 4-5 hours. Continuous intravenous infusion of creatinine and urea was maintained at a rate estimated to replace the loss of these substances in the urine.

Initial experiments on 9 animals showed that towards the end of the period of limb-ischaemia the arterial pressure tended to rise and the urinary excretion to diminish. When the bandages were released, oedema developed in the limbs, the arterial pressure fell very considerably and the urinary flow ceased or else was markedly diminished. The restoration of the blood pressure by the infusion of gum-saline restored the urinary flow to normal, but the creatinine-clearance was only about 30% of its value before the release of the compression. The urine was usually acid, concentrated, and markedly pigmented; the pigment was thought to be haemoglobin, but the presence of myohaemoglobin was not recorded. The chloride content of the urine was not affected in any constant manner.

The hypothesis that a toxic agent, released from the injured limb and passed through the glomeruli, acted on the tubules to produce the renal damage, by virtue of its concentration therein, was tested by a comparison of the two kidneys in the same dog; in one kidney the intra-ureteric pressure was increased, thereby reducing the flow of urine and increasing the concentration of those substances (such as creatinine) which are concentrated by the kidney. In such experiments, where one ureter was partially obstructed at the commencement of the period of limb-ischaemia, and the obstruction was maintained until some hours after the readmission of the circulation into the limb, it was found that the creatinine concentration in the urine from the obstructed kidney was four times as great as that from the unobstructed organ. If the hypothetical poison had been more concentrated on the obstructed side it is argued that the damage also should have been greater there, but in fact the obstructed kidney was found, after removal of the obstruction, to be, if anything, less severely damaged than the other.

The authors conclude from this that, unless it can be assumed that the effect of the poison is fully and immediately

reversible, the hypothesis that the damage to the kidney is due to a diffusible poison which is concentrated in the tubules and produces its effect on the tubular cells in contact with it can be rejected. Some experiments were also carried out to determine if the mere reduction of blood-pressure to 30-50 mm Hg for periods of ½-1 hour would cause renal damage. The production of this by histamine infusion caused anuria, but when the blood pressure was subsequently restored no evidence of renal damage was found.

The kidneys of the animals on which these experiments of crushing had been carried out were flaccid at necropsy, the glomeruli were vascular, and no specific lesion in any part of the nephrons was found on histological examination, in spite of the anuria. In all but one case, no significant mitochondrial changes were found, although they were specially sought.

In their discussion of the mechanism of the renal damage, the authors consider the following possibilities:

- i *Tubular blockage* This was not found on histological examination.
- ii *Low glomerular capillary pressure* The vascular appearance of the kidneys and the low creatinine urine/plasma ratio found when the damaged kidneys secrete at low rate are against this.
- iii *Closure of a proportion of the glomeruli* This, though playing little part in the variation of renal function in the normal mammal, might occur as a reaction to severe injury. No histological evidence for such a change was found. Moreover, tubular diuretics produced an increased creatinine-clearance, which they will normally only effect when the initial creatinine-clearance from the nephrons is abnormally low; the analyses however indicated that the assumption of the lesion in question would be bound to involve unchanged or increased activity in the active units.
- iv *Increase in intrarenal pressure* This is excluded by the flaccidity of the kidneys.
- v *Poisoning of tubule epithelium* This is considered an unlikely explanation on account of the absence of a large and regular increase in urinary chlorides, as well as the absence of an initial polyuria, both of which are found in isolated perfused kidneys poisoned by cyanide or chloral hydrate. The hypothesis was finally rejected as a result of the analysis of the effects of retarding the urinary flow by raising the intra-ureteric pressure.
- vi *Damage to the kidney by exposure to low arterial pressure and consequent anoxaemia* This was excluded by direct experiments.

The authors conclude that no single mechanism will suffice to explain the findings completely and consider that more than one of the factors discussed above may participate. The renal failure might well be due in part to leakage from the tubules and in part to reduced glomerular filtration. With regard to the bearing of these experiments upon the full syndrome of crush injuries in man, it is pointed out that the experiments here described covered only a short period, and the full significance of the findings must await the examination of animals in which the later effects can be studied. Nevertheless the findings are certainly those which might be expected to show themselves in the course of a few hours if the lesions in dog and man are the same. The observations support the recommendation that diuretics should be freely given in the treatment of traumatic anuria.

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LIPIDS OF THE RAT ADRENAL IN SHOCK CAUSED BY EXPERIMENTAL CRUSHING INJURY

by G. Popják, *Journal of Pathology and Bacteriology*, 56, 485-496, October 1944

The author investigated both histologically and chemically the changes in the adrenal lipids during shock caused by muscle-necrosis in rats. It is known from the works of Donahue & Parkins (1934-35), Selve (1936) and others that in conditions of stress or shock produced by various means the adrenal cortex enlarges and, on histological examination, shows depletion of its lipids. Chemical

analyses of the lipid content of the adrenals in shock were lacking

The author of the present paper produced muscle-necrosis in male and female albino rats by binding rubber bands tightly on one hind leg. The tourniquet was released after 5 hours, after which shock developed, similar to that observed by Bywaters & Popják (1942) under the same conditions in rabbits. Twenty-four hours after the crushing injury the adrenals showed a 31–42% increase in weight and a slight but statistically-significant increase in water content. The cause of the adrenal enlargement was probably the increased protein-breakdown associated with muscle-necrosis, as a definite relationship was found between the adrenal enlargement and the volume of dead muscle. Histologically the medulla and zona reticularis showed hyperaemia and in the glands of female rats cortical haemorrhages were also present. Sections stained with Scharlach R showed a marked reduction of stainable lipid material, especially in the zona fasciculata.

Chemical determinations revealed that the histologically observed lipid depletion was due to the loss of cholesteryl esters from the glands, the mean ester-cholesterol content of the experimental glands being less than one-third that of the controls. In the individual experiments, the ester-cholesterol content of the adrenals varied between one-half and one-tenth that of the controls, depending on the extent of the muscle injury. The mean free-cholesterol content of the experimental glands showed a decrease of 37%, i.e. the decrease was of the same order as the increase in weight of the adrenals and was therefore a dilution phenomenon. The neutral fat plus unsaponifiable matter showed a slight increase. The percentage phospholipid content of the ex-

perimental glands was the same as that of the controls. The nitrogen content of the chloroform-extracted (lipid free) experimental glands was less than that of the controls by only 4.8%. Therefore, taking into account the increased weight of the experimental glands, there was an accumulation of phospholipids and nitrogenous substances (probably mostly proteins) in these glands. It was concluded that the increased weight of the experimental glands was brought about by a slight increase in water content, but mostly by the building up of additional amounts of cytoplasm.

When Bennett's (1940) phenylhydrazine test for the adrenocortical ketosteroid hormones was applied to sections of adrenals of the experimental and control rats, it was found that in the former the formation of yellow phenylhydrazones was more marked and more extensive than in the latter. This finding was interpreted that, at the time of cholesterol depletion of the adrenals, there is an increased secretion of adrenocortical hormones, and it is suggested that the rapid disappearance of cholesteryl esters from the adrenals in shock is due to their conversion into the ketosteroid hormones of the adrenal. The author's view is that the role of the adrenals is of only secondary importance in shock, as the animals may die of shock before any changes have taken place in these glands.

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BOOKS, MEMORANDA, REPORTS

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THE FOETAL CIRCULATION AND CARDIOVASCULAR SYSTEM, AND THE CHANGES THAT THEY UNDERGO AT BIRTH

by Alfred E. Barclay, Kenneth J. Franklin and Marjorie M. L. Prichard. Oxford, Blackwell Scientific Publications, Ltd., 1944. 275 pages, 6 plates & 160 illustrations. £2 10s. [£2.5]

Our knowledge of the foetal circulation and cardiovascular system, dependent for more than three centuries on purely anatomical studies and on hypotheses and deductions based upon these anatomical findings, has been revolutionized in the last six years by the application of the method of cine-radiography to an experimental analysis of the circulation in the intact surviving foetus. The brilliant pioneer investigations of the authors in collaboration with Sir Joseph Barcroft and Dr D. H. Barron have revealed the fallacies of the traditional anatomical speculations and replaced them by established factual knowledge based upon the sure grounds of unequivocal experimentation.

The text is divided into five parts. The first part gives a survey of the historical development of the subject. The evolution of ideas about the course of the foetal blood flow is treated in 4 periods: (i) the pre-Harveian anatomical period, (ii) William Harvey's contribution, (iii) the post-Harveian period of functional concepts based on anatomical data, and (iv) the period of experimental research.

Part II deals with the actual course of the blood flow as demonstrated by cineradiography in the cardiovascular system of the adult sheep and mature foetal lamb. The operation for delivery of the foetus by caesarian section is described together with the precautions taken to ensure maintenance of conditions closely approximating to those of the intra-uterine existence of the foetus. Suppression of respiratory reflexes and a minimum of interference with the placental circulation are essential. A short account follows of the cineradiographic technique employed which made possible this first successful study of the foetal circulation by the use of radio-opaque contrast media. Among the significant facts established are the almost complete absence

of mixing of the anterior and posterior caval blood-streams in the foetal right atrium, the terminal bifurcation of the posterior caval stream and the distribution of umbilical and portal venous blood to separate hepatic moieties. The blood returning to the right atrium from the head and neck and forelimbs through the anterior caval channel passes in its entirety through the right atrioventricular orifice into the right ventricle. The posterior caval stream splits within the right atrium so that the major portion of the blood passes through the "via sinistra" into the left atrium and only a minor portion goes to the right ventricle (via dextra). The anatomical and physiological factors determining these directions of flow are described.

The umbilical venous inflow is shown to pass to the posterior vena cava and thence to the heart by two routes: (a) directly by the ductus venosus and (b) indirectly after passage through the larger portion of the liver (umbilical moiety) and certain hepatic veins. The smaller portal venous inflow is also distributed to a well-defined smaller area of liver tissue (portal moiety). On the basis of this vascular organization, both afferent venous distribution and efferent venous drainage, the foetal mammalian liver is divided into two separate anatomical moieties, umbilical and portal. Posterior caval blood entering the left atrium is joined by the not inconsiderable pulmonary venous return, and passes into the left ventricle whence it is ejected into the ascending aorta and distributed mainly to heart, head and forelimbs. The combined anterior caval, coronary sinus and posterior caval blood in the right ventricle is pumped along the conus arteriosus into the pulmonary trunk. A portion passes to the pulmonary vascular bed while the main portion, after passage through the ductus arteriosus, enters

the descending aorta where it joins the residue of the left ventricular output

In the light of the experimental findings some new terms with a more precise functional connotation are proposed to replace the older terminology which had only a descriptive anatomical basis

The sudden dramatic metamorphosis shortly after birth from the foetal to the postnatal circulatory pattern is described. The associated modifications in the umbilical, intrahepatic and pulmonary vascular channels together with the mechanism of functional closure of the ductus venosus, via sinistra and ductus arteriosus are fully analysed

Part III of the book is devoted to a full account of the cardiovascular system of the mature foetal lamb. The course and rate of the blood-flow is detailed. The researches of Barcroft and his co-workers on the oxygen supplies of the foetus and the development of vasomotor and respiratory mechanisms and of the neuromuscular system are reviewed

Part IV embraces an account of comparative anatomical studies in various species of animals, of the placenta, umbilical cord and vessels, hepatic circulation, ductus venosus, posterior vena cava and its terminal bifurcation, and ductus arteriosus. A further chapter gives a summary of work in other species on foetal blood flow and the postnatal closure of the special foetal blood channels

The present state of our knowledge of the anatomy and physiology of the cardiovascular apparatus of the human foetus is considered in part V. The desirability of extending cineradiographic studies to primates and possibly to man is

stressed. The difficulties inherent in such an experimental investigation are fully debated

The significant contributions made by the authors are a striking demonstration of the value of the experimental method and more particularly of the importance of radiographic and especially cineradiographic studies of the normal living subject. They will surely provide an impetus to the further application of these methods to the study of the basic problems of the circulation and other allied aspects of physiology

The text is profusely illustrated. The reproductions of the cineradiographic frames are excellent. A specially commendable feature is the provision of clear and simple coloured diagrams which considerably facilitate the task of the reader unskilled in the complex problem of radiographic interpretation. An excellent bibliography is appended

Chapter headings: (i) historical introduction, (ii) the actual course of the blood flow, determined by cineradiography, in the mature foetal lamb, (iii) the cardiovascular system in the mature foetal lamb, (iv) the circulation in the mature foetal lamb, (v) the birth of the lamb and rupture of its umbilical cord, (vi) the changes occurring during, and shortly after, the birth of the lamb, (vii) comparative anatomy, (viii) comparative physiology, (ix) the cardiovascular system of the human foetus, (x) the course of the blood flow in the human foetus, (xi) certain features of human birth, (xii) circulatory changes occurring during, and shortly after, the birth of the infant, (xiii) concluding remarks, bibliography

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STUDIES OF BURNS AND SCALDS

(Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942-43) Medical Research Council, Special Report Series No 249. London, H.M. Stationery Office, 1944. 210 pages, 50 illustrations. 4s [£0.2]

In the four years immediately preceding the war there were approximately 1,270 deaths per annum from burns and scalds in England and Wales, of which nearly half were at ages under 15. In the present war, burns and scalds have become still more important, and their treatment one of the major problems of war surgery. These injuries present many unsolved problems. It is not clear why damage to the skin (sometimes, in children, involving only a tenth of the body surface) should so often prove fatal, nor has it been possible up to now to prevent septic infection of most of the deep burns. Skin replacements by grafting procedures has greatly assisted healing, but the possibility of improved methods needs to be explored. There are also difficult metabolic problems created by the long-continued suppuration and exudation from the burned surfaces, and by the destruction of skin tissues

The need for investigation of all these questions has long been recognized, but progress has always been slow, hampered by the fact that burns and scalds occur at irregular intervals and that the patients are received into every general hospital. Nowhere in Britain had there been hitherto a concentration of patients together with a team of surgeons and laboratory workers for a prolonged systematic study

In view of the urgent need created by the war to initiate further research on various aspects of the treatment of burns, the Medical Research Council, in co-operation with the Royal Infirmary, Glasgow, established a laboratory team with a view to a preliminary bacteriological, haematological and biochemical survey of the problem. The Royal Infirmary, Glasgow, was chosen, as some of its wards have for many years been set aside for the treatment of burns, and a larger number of these injuries is dealt with there than at any other hospital in the British Isles. Dr Leonard Colebrook directed the laboratory studies, co-ordinating them with the clinical observations. Professor J. W. S. Blacklock arranged laboratory facilities for the team and supervised the pathological investigation of the cases. The reports comprising this monograph embody observations made in 1942 and 1943 on some 400 in-patients with burns and nearly 2,000 patients with less-severe burns, who were treated as out-patients

The work covered by the reports deals chiefly with two aspects of the burns problem—the control of infection and the treatment of ‘burns shock’. Part I describes an attempt to formulate the functions of an ideal first-aid treatment: calls attention to the danger of first-aid undertaken without regard to asepsis, recommends an antiseptic cream for use in certain limited circumstances and sets out the results obtained in combined clinical and bacteriological trials of the cream. Part II challenges the generally accepted view that the infection of deep burns is inevitable: it emphasizes the large part played by cross infection and describes the measures taken to prevent it, including the elimination of reservoirs of infection by penicillin and the sulphonamides. It shows the degree of success achieved by these procedures and discusses the lines along which further progress may be expected. Part III deals with replacement therapy, and attention is focused upon ‘burns shock’, which is responsible for the majority of deaths from burns. Part IV supplements Part III and provides data on the haemoconcentration with different degrees of burning. It

traces the development of anaemia in burned patients and supplies evidence that this is not merely the result of a compensatory dilution of the blood by the return of fluid from the tissues. Striking changes in the fragility of the erythrocytes in severely burned patients are also recorded. Part V presents a preliminary survey of some of the biochemical changes found in a series of 70 burned patients. Part VI records post-mortem findings in 30 fatal cases of burns and supports the current view that extensive central lobular necrosis of the liver is usually associated with tannic-acid treatment.

Contents: Part I. The first-aid treatment of burns and scalds (L. Colebrook, T. Gibson & J. P. Todd). Part II. The control of infection in burns and scalds (L. Colebrook, A. M. Clark, T. Gibson & J. P. Todd). Part III. Replacement therapy in burns shock (T. Gibson & A. Brown). Part IV. Blood changes and blood pressure in burned patients (A. Brown). Part V. Chemical changes in the burned patients (A. B. Anderson & E. Semeonoff). Part VI. Post-mortem findings in thirty fatal cases of burning (T. Gibson)

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THE TREATMENT OF “WOUND SHOCK”

(Instructions Produced by the Medical Research Council Committees on Traumatic Shock and on Blood Transfusion, in Co-operation with the Army Medical Service)

Medical Research Council, War Memorandum No 1. Second edition. London, H.M. Stationery Office, 1944. 32 pages, 5 illustrations. 6d. [£0.025]

This, the first Medical Research Council war memorandum, appeared originally in 1940, and has been several times reprinted. Fresh evidence, changing points of emphasis, and new modifications of the therapeutic procedure, have necessitated the re-writing of almost all the original memorandum. Recent investigations on ‘shock’ have served not only to clarify various aspects of the problem but also to emphasize the complexity of the subject, in this memorandum stress has therefore been laid on the non-specific nature of the ‘shock’ syndrome, upon which there is still need for intensive clinical and experimental research.

The memorandum discusses the general effects of injury (‘shock’), mechanisms in oligæmic ‘shock’ from hæmorrhage, vasovagal collapse, effects of tissue trauma, other complicating factors (fat embolism, toxic gases, infections, anaesthesia, dehydration), treatment. Appendices describe the Army and the Medical Research Council blood transfusion outfits

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INDUSTRIAL MEDICINE

Second Interim Report, January 1945, of the Social and Preventive Medicine Committee, Royal College of Physicians of London. 24 pages

In its previous interim report the Social and Preventive Medicine Committee appointed by the Royal College of Physicians of London considered the teaching of social and preventive medicine and the arrangements for social medicine inside the hospital. The committee has given much time to the consideration of the

aspect of social medicine outside the hospital, namely industrial medicine, and thus second report is concerned solely with that subject

After devoting some space to the historical background of industrial medicine and to legislative measures in connection with it, the report considers the scope of the existing medical services available to industrial workers. It is pointed out that, while the larger factories are adequately provided with medical supervision, more than half the workpeople in Britain are employed in factories with less than 250 operatives, in which medical supervision is adequate in only a few instances. In the opinion of the committee, one of the immediate requirements of the people of Britain is an industrial health service which includes provision for all who need it most, not only the large industrial concerns but also the small factories and workplaces, the building industry, transport services, etc. In fact, the industrial health service of the future must be comprehensive, and national in scope.

The aims of an industrial health service should be (a) to promote the general health of the worker by the provision of a good working environment and by fitting the worker into that environment, (b) to prevent occupational disease, (c) to assist in the prevention of injuries at work, (d) to organize and supervise a service for the emergency treatment and care of injured and sick workers at their place of work, (e) to take an active part in the restoration to full capacity of workers disabled by injury or disease, and resettlement of workers suffering from permanent disability, (f) to educate the workers in the preservation of health and promotion of well-being, (g) to promote research and investigation. The industrial health service should be primarily concerned with working environment, and for this purpose continuous investigation is necessary, in co-operation with other departments of management.

The organization of an industrial health service should be an integral part of the proposed national health service. Administration should be the responsibility of the Ministry of Health, with the delegation of certain administrative and executive functions to the Ministry of Labour and National Service and other bodies.

The report considers the staffing, terms of service and finance, and appointments to an industrial medical service. The training of medical officers requires careful planning. For those undertaking part-time service, "there would appear to be a need for a short course, lasting perhaps six weeks, when the main principles of industrial medicine and hygiene can be intensively explained and taught together with visits to factories and industrial undertakings. Such short courses, combined with even shorter refresher courses from time to time, would provide the basic interest and training which could then be extended by working experience under more senior medical officers."

"For the medical man or woman who wishes to take up industrial health as a career and to become a whole-time industrial medical officer, a more comprehensive training is required. In the opinion of the committee it is essential that this training should be founded on the study of preventive and social medicine, in order to avoid too narrow specialization. The special course of instruction in industrial health should be preceded by at least two years' post-graduate experience in medicine, of which not less than one year should be spent in general practice.

Whether a special diploma in industrial health is instituted or not, there should be a well designed course of academic and practical training of one year's duration. It should begin with a basic course in preventive medicine which might be taken in common with candidates for the diploma in public health, and then proceed to a period of more specialized study, including a short clinical course in industrial medicine as well as teaching and practical experience in the problems of industrial health.

The main advantage of instituting a diploma in industrial health is that it would tend to establish a minimum standard of training and qualification which could be recognized and understood by industrial firms. The chief disadvantages are that the multiplication of diplomas is apt to cause confusion, and that it would be very difficult to plan a syllabus to cover the many and varied aspects of industrial medicine, with the risk that the diploma would become based upon a course of instruction too stereotyped and too elementary to be of much value.

It is probably advisable that the granting of any diploma in industrial health be restricted as with other diplomas to the Royal [Medical] Colleges, but the Universities might well consider making industrial medicine an alternative subject for the M.D. degree." [The British M.D. is a higher degree. The British M.B. corresponds to the M.D. of most other countries.]

The important work being carried out by the Industrial Health Research Board is mentioned, and the continuing need is stressed for such a body, responsible for investigating problems of national significance and, in addition, problems relating to local industries which cannot be carried out owing to lack of special facilities by research teams in the various regions.

In the light of the views and arguments set out in this report, the committee makes the following recommendations:

- i That an industrial health service be planned as an integral part of the national health service with arrangements for close association at all levels, central, regional and local, with other branches of the national health service.
- ii That such an industrial health service should be national in its scope and apply to every variety of employment.
- iii That such an industrial health service be staffed by medical inspectors, consultants in industrial medicine, whole-time and part-time medical officers, together with the necessary non-medical personnel, all of whom will have received training suitable for the type of work undertaken. Proposals for such training are indicated in the report.
- iv That the essential feature of administration of an industrial health service should be a close association everywhere with

the body responsible for the peripheral administration of the national health service and with university departments of industrial health, where such exist.

- v That clinical facilities, including beds for the consultants and research workers in industrial medicine, should be provided.
- vi That the aims of such a service should include the promotion of the general health of the worker by the provision of optimum environmental conditions and by fitting the worker into such conditions, the prevention of disease and accidents in industry, the taking of an appropriate share in the rehabilitation of the disabled workman, and the education of the workers in the preservation of health and promotion of well-being.
- vii That research in industrial health should be given every possible encouragement administratively, and by the industries themselves.

The report is signed by Lord Moran, President of the College

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RECENT ADVANCES IN ENDOCRINOLOGY

by A. T. Cameron. Fifth edition. London, J. & A. Churchill, 1945. 415 pages; 73 illustrations. 18s. [£0.9]

The *Recent Advances* series of monographs devoted to reviews of recent developments in the various branches of medicine and cognate subjects has for a number of years enjoyed a well-deserved reputation. Each volume is written by a leading authority, and is well produced and illustrated.

The volume devoted to recent advances in endocrinology is no exception. It is written by the professor of biochemistry at the University of Manitoba. In the present edition more attention has been paid to the clinical aspects of endocrinology. As the author points out, the publication of papers on the subject has not diminished, in spite of the European war, nor has inaccessibility to literature published in enemy countries much lessened the task of reviewing new material. The literature to the end of 1943 is reviewed, and there are a few references to papers published in 1944. Important recent advances reviewed in the book include the use of radioactive iodine in the study of thyroid function, the various iodized protein preparations having thyroid activity greater than the thyroid itself, the function of the parathyroid hormone and its relationship to phosphate excretion, the steroid hormones of the adrenal cortex, new synthetic oestrogens, the newer knowledge of Cushing's and Fröhlich's syndromes. The book is well illustrated and there are comprehensive lists of references to each section and an adequate index.

Chapter headings: (i) introduction, (ii) the thyroid gland, (iii) disease states associated with abnormal thyroid function, (iv) the parathyroid glands, (v) the islets of Langerhans and insulin, (vi) the steroid hormones and related compounds, (vii) the adrenal glands, (viii) the endocrinology of reproduction, (ix) the pituitary gland, (x) diseases correctly and incorrectly associated with hypofunction of the anterior pituitary, (xi) gigantism and acromegaly, (xii) Cushing's disease and the adrenocortical syndromes, (xiii) some other hormones and some related problems.

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PSYCHOLOGY AND PSYCHOTHERAPY

by William Brown. Fifth edition. London, Edward Arnold & Co., 1944. 223 pages. 14s. [£0.7]

Chapter headings: (i) introduction, the present importance of psychology and psychotherapy, (ii) characteristics of dissociation, (iii) degrees of dissociation, multiple personality, (iv) Freud's theory of dreams, (v) Freud's theory of the unconscious, (vi) theories of emotion, (vii) the psycho-neuroses of war, (viii) factors in psychotherapy, (ix) psychotherapy in the prevention and treatment of alcoholism, (x) psychology and the adolescent, (xi) the control of sex, (xii) psychological problems of later life, (xiii) sublimation and spirituality, (xiv) suggestion, hypnotism and faith, (xv) the psychology of personal influence, (xvi) the psychology of peace and war, (xvii) the psychology of modern Germany, (xviii) relation of mind to brain, (xix) psychical research, the eternal values. Appendix. Record of a deep mental analysis (psycho-analysis).

The object of the author in writing this book has been to give the general reader a grasp of the position and achievements of present-day psychology and psychotherapy, and to provide him as well with a psychological basis for the study of politics and of international relations.

In chapters ii-vi Dr Brown gives a critical review of the various theories on which the different schools of psychology are based, Freud's theories of dreams and of the unconscious are described in detail. Chapters vii-x outline the methods used in psychotherapy—the practical application of the theories already stated. Here the author's experience in this work, extending over a period of 30 years, gives authority to his comments and criticisms.

Chapter xi is new in this edition and from this point onwards Brown the philosopher, with his sense of spiritual values, takes precedence over Brown the psychologist. Chapter xvii is also new, and here the author seeks to trace, in the various German philosophers, the roots of what has become the world's problem to-day. The relevance of this chapter to the remainder of the book is not obvious, and most of its substance has been previously repeated *ad nauseam* in the popular press. Chapter xviii sums up the views of psychologists and philosophers on the relation of mind to brain, showing the stage they have reached and indicating the fundamental importance of this aspect of the search for knowledge and understanding. The final chapter includes an unusual

feature—a review of the position of psychical research. The appendix contains a patient's own record of his experience during deep analysis. There is a short bibliography and a good index.

Although the reader will no doubt disagree with some of the author's statements, the book is a most interesting and stimulating survey of psychological and psychotherapeutic ideas and their application. A review of the previous edition concluded that "whatever posterity may think of the scientific merits of books like this, to the future historian it will represent a typical line of thought in psychological medicine between the two wars."

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RECTAL SURGERY

A Practical Guide to the Modern Surgical Treatment of Rectal Diseases

by W. Ernest Miles. Second edition. London, Cassell & Co., Ltd., 1944. 359 pages, 107 illustrations. 17s. 6d. [£0.875]

The author of *Rectal surgery* is recognized as an outstanding authority on his subject, and although the book is written as a record of his own interpretation of the various problems presented to him by rectal disease and an outline of the methods of treatment which in his experience have proved to be most efficacious, it is at the same time an excellent general introduction to the subject. Comparatively little recent literature on rectal surgery is available, apart from general principles incorporated in textbooks of surgery.

Behind the writing of this book is a lifetime of experience which will be of inestimable value to students, although the author himself is careful to point out "that there is a limit to knowledge that can be gained from the reading of books and that the best book of all is the one whose leaves are represented by the patients in the out-patient clinics and wards of hospitals devoted to rectal surgery."

The author is a strong advocate for radical measures in malignant disease of the rectum, and he deplors the modern tendency to conservatism. His observations on ano-rectal fistulae have led him to classify these fistulae according to the relationship of the original abscess cavity to the musculature of the anal outlet, to point out that the type of fistula is determined by this relationship and to establish the fact that ano-rectal fistulae differ in type. The appreciation of this fact will, he hopes, be instrumental in abolishing the disastrous consequences of some operative measures.

Throughout the book prominence is given to differential diagnosis. Details of operative technique and methods of post-operative treatment closely follow the author's original methods.

Chapter headings: (i) anatomy, (ii) ano-rectal abscess, (iii) ano-rectal fistulae, (iv) perineal fistulae of non-ano-rectal origin, (v) fistulous communications between the rectum and the interior of neighbouring organs, (vi) external piles, (vii) haemorrhoids or internal piles, (viii) anal fissure, (ix) prolapse of the rectum, (x) intussusception of the rectum, (xi) pruritus ani, (xii) malignant growths of the anus and rectum, (xiii) benign tumours of the anus and rectum, (xiv) ulceration of the anus and rectum, (xv) stricture of the anus and rectum.

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TEXTBOOK OF ANAESTHETICS

by R. J. Minnitt & J. Gillies. Sixth edition. Edinburgh, E. & S. Livingstone, Ltd., 1944. 486 pages, 199 illustrations. £1.5s. [£1.25]

It is 25 years since this book first appeared, under the title of *Handbook of anaesthetics* and written by J. S. Ross. Later editions were prepared under the authorship of H. P. Fairlie and R. J. Minnitt. The book has grown both in size and authority during successive editions and now is properly renamed *Textbook of anaesthetics*. The senior author, who is lecturer in anaesthesia, University of Liverpool, already enjoys a considerable reputation as an anaesthetist; J. Gillies is consultant in anaesthetics, Department of Health for Scotland, and anaesthetist to the professional surgical unit, Royal Infirmary, Edinburgh.

Extensive revision has taken place in the present edition. There are new chapters on trichlorethylene, endotracheal anaesthesia, intravenous anaesthesia and anaesthesia for dentistry. A chapter on local and regional anaesthesia, contributed by L. B. Wevill, includes a section by J. Boyes on its application to dentistry.

This is a sound, practical book, essentially for the beginner. Production and illustrations are of a high standard and there is a very full index.

Chapter headings: (i) anaesthetic drugs, (ii) inhalational methods of administration, (iii) changes in the blood gases, (iv) shock and anaesthesia, (v) clinical observation of the patient, (vi) preparation of the patient, (vii) premedication and basal narcosis, (viii) posture of the patient, (ix) nitrous oxide, (x) ethylene, (xi) cyclopropane and closed circuit, (xii) ethyl ether, (xiii) di-vinyl ether, (xiv) ethyl chloride, (xv) chloroform, (xvi) trichlorethylene, (xvii) endotracheal anaesthesia, (xviii) intravenous anaesthesia, (xix) anaesthesia for dentistry, (xx) analgesia and anaesthesia in obstetrics, (xxi) the accidents of anaesthesia, (xxii) the sequelae of anaesthesia, (xxiii) therapeutic use of oxygen, etc., (xxiv) choice of anaesthetic, (xxv) local and regional analgesia.

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PHARMACOLOGY

by J. H. Gaddum. Second edition. London, Oxford University Press, 1944. 160 pages, illustrated. £1.1s. [£1.05]

This excellent book is written primarily for medical students and it therefore takes into consideration the requirements of

examiners. But its outstanding merit is that it will give to those students who use it as a textbook a good conception of the principles and methods of pharmacological science. Facts with immediate practical applications receive special emphasis, but some other facts are included, since one purpose of the book is to supply a background to the experimental methods which have led, and are still leading, to the introduction of so many new therapeutic drugs. The second edition of the book has been carefully revised, a number of references to the literature, chiefly of reviews, have been added. Another addition is a short key to the interpretation of chemical names, and the needs of veterinary students have been borne in mind by the addition of some veterinary facts. The book covers all important aspects of drug action and includes some information not readily available elsewhere. It is very well written, with a good index, and its production leaves nothing to be desired.

Chapter headings: (i) diet, inorganic salts and fats, (ii) vitamins, (iii-iv) hormones of known structure, (v) central nervous system stimulants, (vi) narcotics, (vii) the brain, (viii) body temperature, (ix) sensory nerves, (x) motor nerve-endings, (xi) muscles, (xii) the alimentary canal, (xiii) circulation, (xiv) blood, (xv) kidney, (xvi) respiration, (xvii) proteins, (xviii) toxic elements, (xix) drugs which destroy life, (xx) chemotherapy, worms and protozoa, (xxi) chemotherapy, bacteria, (xxii) general pharmacology.

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BRITISH EMPIRE CANCER CAMPAIGN

Twenty-First Annual Report, 1944

published by the British Empire Cancer Campaign, 11 Grosvenor Crescent, London, S.W. 1. 95 pages. 12s. 6d. [£0.625]

Five years of war have not materially hindered the study of cancer in Britain; this report is, in fact, able to record substantial progress of the knowledge and treatment of the disease. Mr. J. P. Lockhart-Mummery, honorary secretary of the British Empire Cancer Campaign, has edited the report and has contributed a summary of its various sections.

Carcinogenic agents. Considerable progress has been made towards explaining the remarkable carcinogenic properties of 2-acetylaminofluorene. As the result of administration of this compound, workers at the University of Sheffield were able to produce mammary tumours in male and female rats. It is probable that these tumours are due to interference with liver function, bringing about a failure to destroy an excess of endogenous oestrogen, and that the resultant hyperplasia of breast-epithelium is the proximate cause of mammary cancer induced by acetylaminofluorene. It has also been possible to localize the carcinogenic action of acetylaminofluorene to a site not usually affected. Both benign and malignant tumours of the thyroid have been obtained by the combined action of acetylfluoramine and allylthiourea. At the Sir William Dunn School of Pathology, Oxford, an experimental study of the effect of various polycyclic hydrocarbons on various species of animals has led to the discovery that, unlike other hydrocarbons so far tested, 9,10-dimethyl-1,2-benzanthracene is highly carcinogenic to the rabbit's skin. A method of fluorometric estimation of benzyrene, developed at the Cancer Research Laboratory, Royal Victoria Infirmary, Newcastle-upon-Tyne, and already described in previous reports, has been further studied. At the Mount Vernon Hospital epidermal tumours have been produced in mice by a single application of benzyrene if the skin is previously or subsequently treated with a non-carcinogenic agent which causes epithelial proliferation. Following the discovery that prolonged administration of pure β -naphthylamine to dogs has resulted in the appearance of papillomatosis and cancer of the bladder, other compounds used in the dye industry and suspected of playing some part in the causation of cancer of the bladder are now being studied at the department of experimental pathology, University of Leeds.

Chemotherapy. Study of the relation between chemical structure and the growth-inhibiting action of synthetic compounds shows that a large number of substances possessing appreciable inhibitory activity embody the carbon skeleton of a *sym*-diphenylethylene. At the Royal Cancer Hospital a considerable number of compounds based on the simple prototype *sym*-diphenylethylene have been examined; several have proved especially active and the results taken together show the controlling influence of very small alterations in molecular structure. From the same hospital an account is given of a clinical investigation of the growth-retarding activity of the synthetic oestrogens triphenylchloroethylene, triphenylmethylstyrene and stilboestrol. Of 22 cases of late cancer of the breast treated with triphenylchloroethylene, 10 showed a significant although temporary retardation of the growth of the tumour. Of 14 cases of carcinoma of the breast treated with stilboestrol 5 showed alterations in the growth and behaviour of the tumour similar to those produced by triphenylchloroethylene. At the Middlesex Hospital a large series of cases of carcinoma of the prostate is now under treatment with various doses of stilboestrol, hexoestrol and dienoestrol and the effect on the acid serum-phosphatase and the x-ray picture is being closely watched. Up to the present the results completely confirm the view previously stated that many patients suffering from prostatic carcinoma can be rendered symptom-free and can be so maintained for long periods.

Filterable agents and viruses. One of the peculiarities of virus-induced sarcomata in fowls is their tendency to spontaneous retrogression in a minority of experimentally-infected birds. This tendency has been studied for a number of years at the Glasgow Royal Cancer Hospital. It is suggested that the malignant change is not irreversible.

Pathology In attempts to ascertain the nature of the substance responsible for the pronounced leucocytosis and associated tissue-changes which may accompany the growth of sarcomata in mice, workers at the cancer research department, London Hospital, have found that closely similar changes occur in mice bearing a reticulosarcoma and in mice treated with a mixture of pentose nucleotides. Preliminary observations in other experiments suggest that two nucleotides, guanylic acid and adenylic acid, exert a growth-inhibitory action. Experiments were carried out in the department of bacteriology and pathology, University of Glasgow, to decide whether the presence of a malignant tumour lowers the general resistance to pyogenic infection. Tumour-bearing mice were inoculated with virulent staphylococci and then treated with a sulphone and antitoxin, and an increased mortality-rate was observed among these mice as compared with controls, indicating that the tumour increases the host's susceptibility to pyogenic infections, even when the general health is apparently good. At St Mark's Hospital, an analysis of 1,000 cases of rectal cancer treated by radical excision has shown that 40% of patients were alive after 5 years. Deaths from recurrence after this period were very rare. Treatment of rectal cancer by colostomy showed only a very low survival-rate.

Radiobiology At the Molteno Institute, Cambridge, further steps have been taken in the unification of knowledge of the effects of ionizing radiations on viruses and enzymes. Ionization either inside the virus molecule or in the solvent can cause inactivation of the virus. Enzymes can be inactivated directly when in the dry state and indirectly in solution. Further work is being carried out, with enzyme solutions of different strengths, to study the transition between these two effects. The degree of indirect inactivation has been shown to be greatly influenced by the quality of the ionizing radiation. Multiple biopsies from 24 squamous-cell carcinomata of the cervix, examined at the Institute of Animal Genetics, Edinburgh, have shown that the rate of division as well as the proportion of differentiated and potentially dividing cells varies in different regions of a tumour. Evidence is presented to show that the efficiency of radiation cannot be estimated by an alteration in the division-rate alone, but induced chromosome abnormalities can be used as a measure of radio-sensitivity of a tumour. At the Strangeways Research Laboratory, Cambridge, quantitative observations on the effect of x- and γ -rays on tumours of the cervix have been continued, and the work has been extended to a study of the response to radiation of malignant growths of the tongue and oral cavity. The significant biological factor for successful radiotherapy of these tumours appears to be a capacity of tumour cells for differentiation. In the series of cervical tumours it was found that an increase in dose was not correlated with improvement of results in the differentiating types of growth, but was correlated with some improvement in the case of the more anaplastic types. In view of the importance of the ultra-short electromagnetic waves in treatment by diathermy, investigations have begun in the cancer research department, Westminster Hospital, on the absorption of these waves by tissues and tissue fluids.

Radiotherapy Workers at the Mount Vernon Hospital and Radium Institute have shown that the growths which give the most satisfactory ultimate response are those which are well-differentiated, and conversely that the anaplastic type has a greater tendency to recur. At Westminster Hospital the radiation treatment of osteoclastoma is giving promising results, most cases show a satisfactory response to dosages of 2,000 röntgens.

Statistics The Clinical Cancer Research Committee presents this year a detailed analysis of 1,405 cases of cancer of the stomach. The ratio of males to females was three to two, and the mean age at onset was 60 years in both sexes. An analysis of the occupations of 656 male patients compared with the 1931 Census figures for Greater London showed a close correspondence, except in the case of clerks and typists, amongst whom the incidence was only one half of that expected. Although 52% of the patients had been sent to hospital within three months of the first consultation, it was found that 19% had been kept under medical treatment for over three months before being referred for investigation. Forty-nine per cent of all cases underwent laparotomy, but a radical operation was possible in only 17%. Of 241 gastrectomies, only 22% were performed whilst the symptoms were of less than three months' duration, and 40% of less than six months' duration. The survival-rate after radical operation in the early stages, before the regional lymph nodes were involved, gave, on the basis of a 4-year period of observation, an expectation of life of 65-70%. In the later stages the rate fell to 49% and, when only a palliative operation was possible, to 40% of normal. These figures emphasize the urgent necessity of early investigation of gastric symptoms in patients over 50 years of age.

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HEALTH RESEARCH IN INDUSTRY

Proceedings of a Conference on Industrial Health Research held at the London School of Hygiene and Tropical Medicine, September 28, 1944. Published by the Industrial Health Research Board, Medical Research Council. London H.M. Stationery Office, 1945. 27 pages. 6d. [£0 025]

Sir Edward Mellanby, chairman at the opening session of this conference, reviewed the work of the Industrial Health Research Board. In 1942 the Medical Research Council, the parent body,

reconstituted the Board, including in its terms of reference not only the type of work it has been doing previously, namely discovery of the best conditions for the maintenance of health and efficiency in industry, but also the whole subject of industrial medicine and disease. Some of this work had previously been undertaken by the Medical Research Council. A new department of industrial medicine was set up at the London Hospital under Dr Donald Hunter.

A great amount of research has been directed to the care and efficiency of the Armed Forces, and personnel research committees have been set up for each of the fighting services with the object of studying the men in relation to their tasks, in fact to fit the men to the machines or the machines to the men. Many investigations on the psychological aspect of these problems have been carried out by the recently constituted Applied Psychology Unit at Cambridge.¹ The Board recently published the report of its committee set up to investigate the recording of sickness absence in industry.² Much work, as yet unpublished, has been done on atmospheric pollution in filling-factories, new methods of sampling TNT, comparative efficiencies of dust-sampling instruments, and the best method of using overhead heaters in factories. Many investigations have been directed to lighting problems, and the Board are preparing a report covering the work on this subject during the past 25 years. Another type of investigation which is being made on a large scale is directed to the discovery of the incidence of psychoneurosis in industry.

Sir Edward Mellanby referred also to the work by Dr Leonard Colebrook on the treatment of burns, the enquiry by Professor A. A. Miles into the place of infection in industrial injury—to see, for instance, whether this actually takes place at the time of injury, or at the first dressing or in the hospital, and the work of Dr R. T. Grant on the study of traumatic shock.

Dr Donald Hunter gave a brief description of the department for research in industrial medicine at the London Hospital, the first of its kind in Britain. Since its inception, the department has carried out investigations on industrial poisons, pneumoconioses, boiler-makers' deafness, and other industrial diseases. Dr Hunter pleaded for the co-operation of industrialists in the efforts now being made to improve conditions in industry and in supporting the universities and hospitals by endowing chairs of industrial medicine.

The second session of the conference was opened by Lord Forrester with a paper on industrial research from the point of view of management. Lord Forrester considered that much research remains to be carried out on the problem of posture in industry, on industrial health and personnel records, on the problem of working time, breaks in working hours and the organization of shift work, on sanitary accommodation for workers, and on the relationship of the physical environment of industry itself with the environment around it. In this last connection the speaker pleaded for better lay-out, materials, services, design and structure in factory buildings.

Mr G. A. Isaacs addressed the conference on "Industrial health research from the point of view of the trades unions" and Dr K. J. W. Craik described the work of the Applied Psychology Research Unit set up at Cambridge University by the Medical Research Council, and at present occupied principally on problems arising from the war. The principles upon which the Unit has been working are of suiting the job to the man, of suiting the man to the job, and of improving the man's performance.

¹ [see BMB 615]

² [BMB 606/94]

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MINIATURE MASS RADIOGRAPHY OF CIVILIANS

For the Detection of Pulmonary Tuberculosis. By K. C. Clark, P. D'Arcy Hart, P. Kerley and B. C. Thompson. Medical Research Council, Special Report Series No 251. London, H.M. Stationery Office, 1945. 135 pages, 51 illustrations. 3s. [£0 15]

This report, published by the Medical Research Council, deals with the first 23,000 civilian examinations made by mass miniature radiography after its official introduction into Britain. The method had been used in the Fighting Services for some time, and in 1942 an apparatus was approved by the Ministry of Health for civilian use. This instrument was portable and was designed for use in factories and other places where large numbers of people were available for examination, the examination was entirely voluntary. The groups examined included factory and office workers and patients in a mental hospital. It was found that about 5% of apparently normal persons had shadows in the miniature film which were regarded as suspicious and which required a full size radiograph for their interpretation. About half of these persons were found to have no abnormality when the larger film was examined. Among the others, tuberculous lesions were found amounting to about 1.3% of the total number of persons examined and the incidence of clinically active tuberculosis was about 0.4%. This incidence was higher among those who were known to have been in contact with the disease.

The report deals in great detail with every aspect of the practice of mass radiography. Part I consists of a guide to administration and technique of mass radiography, including the handling of the apparatus and the processing of the films. Part II gives the results of the Medical Research Council survey of mass radiography, 1943. There are 7 appendices and a number of useful illustrations.

GUIDE TO THE JOURNALS

Two important British periodicals made their first appearance in 1944

The first, the *British Journal of Industrial Medicine*, is intended for the publication of original work on industrial medicine. It is published quarterly by the British Medical Association, and is edited by Dr Donald Hunter, of the department of research in industrial medicine, London Hospital. All parts of the *British Journal of Industrial Medicine* published to date have been noted in *BMB* 'Guide to the Journals'.

The second, the *Proceedings of the Nutrition Society*, now in its second volume, is noted for the first time in this issue of *BMB*. The Nutrition Society was formed in 1941, its main object being to provide a common meeting place for workers in the varied fields of nutrition—physiological, biochemical, agricultural, medical, sociological, economic and public health. The *Proceedings of the Nutrition Society* the publication of which was made possible by the generosity of the Royal College of Physicians of London, is edited by Dr S. K. Kon. National Institute for Research in Dairying, Reading. The honorary secretary of the Nutrition Society is Dr L. J. Harris of the Dunn Nutritional Laboratory, Cambridge.

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The importance of chemical contributions to medicine is well recognized. The fruitfulness of the chemical approach to medical problems is reflected in the many developments of biochemistry and in the introduction of the synthetic remedial agents which have now become indispensable to medical practice. Yet up to the beginning of the nineteenth century, medical writers were preoccupied with mechanical doctrines, with consequent emphasis on the "solids" of the body, and it was not until the second decade of the nineteenth century that the isolation of active principles of drugs—"proximate analysis" as it was then called—showed the way to the modern era of chemical medicine which, perhaps because some of its products are of immediate interest to every medical practitioner, has overshadowed the medical implications of physics.

Nevertheless physics has, in recent years, begun to influence medicine to an increasing extent, and it was thought that it might be interesting to survey this relatively unfamiliar field in a number of this Bulletin. However, after preliminary discussions with several physicists, and particularly with Professor W V Mayneord, it became clear that only a very incomplete picture could be presented in a single number. It was therefore decided to distribute the material over several numbers to be published at irregular intervals. The present number is the first, and probably the shortest, of the series. It has no very practical objective, but it contains matter of relevance to many branches of medicine.

DR. W V MAYNEORD, who contributes the introductory article to the series, is director of the physics department of the Royal Cancer Hospital (Free) and professor of physics applied to medicine in the University of London. His work has been concerned chiefly with the measurement of x and gamma rays for therapeutic purposes. Dr Mayneord has published a number of papers on the physical foundations of medical radiology, and he was also associated with the discovery of carcinogenic hydrocarbons.

DR. H. HURST is a senior research member of the department of colloid science, Cambridge. He was formerly studying the mode of action of insecticides in the department of zoology and applied entomology of the Imperial College of Science, but was seconded to Cambridge for work in connection with insecticides used in mosquito control. For some years Dr Hurst has been developing a new approach to the study of drug actions, originating from the discovery that the toxicity of mixtures of insecticides may be far greater than the sum of the toxicities of their separate components. Most of Dr Hurst's papers on this subject have been published in

Nature. The demonstration of the selective action of the tissue lipoproteins on enzyme activity opens a new perspective in a complex field of investigation in which attention has hitherto been directed mainly towards the examination of purifying enzyme systems.

DR. G. E. DONOVAN graduated in Ireland, where he obtained degrees both in medicine and science. After several resident hospital appointments he entered the public health service, and is now a medical officer of health in Wales. He had previously done research work on phonocardiography in the physiology department of the National University of Ireland, and has continued to make a special study of electrical measuring apparatus used in biology and medicine. He has published a number of papers on electrical methods of graphic registration, and also on the electron microscope.

DR. DAVID S. EVANS was trained as an astronomer and mathematician and before the war was engaged on spectroscopic studies at the university observatory, Oxford. During the war he has collaborated with Dr K. Mendelsohn on the application of physics to medical war problems. He is an experienced broadcaster on scientific subjects, and is advisory editor of the scientific monthly *Discovery*.

DR. K. MENDELSSOHN is a physicist who has worked since 1933 at the Clarendon Laboratory, Oxford. His main line of research has been the investigation of the properties of matter at temperatures near absolute zero. Since the outbreak of war he has devoted most of his time to the solution of physical problems connected with medical work. He has participated in the development of a semi-automatic anaesthetic machine (the Oxford Vaporiser) and has designed (with D S Evans and F Barnett Mallinson) a blood-pressure indicator for use in the operating theatre. During the last years he has been chiefly engaged (in collaboration with the Nuffield department of clinical medicine, Oxford) on the investigation of the physical factors underlying heat-treatment in clinical practice.

DR. A. H. S. HOLBOURN is a physicist who began research on the properties of light in 1931, at the Clarendon Laboratory, Oxford. Since 1939, he has been engaged on work at Oxford with Professor H. W. B. Cairns, the Nuffield professor of surgery. This work has involved a study of the physical mechanisms which produce damage of the brain as a result of blows to the head, and such collateral problems as the design of crash-helmets for motor-cyclists.

SPECIAL CONTRIBUTIONS

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PHYSICS IN MEDICINE

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During the last fifty years discoveries and developments in physics have intruded so far into medicine that physical methods of treatment and diagnosis have become indispensable, yet physics still hovers a little uncertainly on the fringes of medical research, education and organization. This is not surprising when one considers that physics is the most highly developed and abstract of the fundamental sciences, and the practice of medicine the most highly developed of the social arts. Numerical precision, mathematical analysis and consequent extreme generality and abstraction are the distinguishing marks or, at least, implied ideals of physics, while in medicine the individual patient and his often incomprehensible complexities fill the picture, sometimes to the exclusion of general principles and more abstract erudition. Yet it is recognized more and more clearly that physics has now an important part to play in medical research and even in the daily treatment of the patient. Correspondingly, physics itself might benefit immensely from closer contact with the medical and biological problems awaiting solution.

Some Applications of Physics in Medicine

The most striking and perhaps best known of the recent applications of physics in medicine lie in the sphere of medical radiology, that is particularly in the applications of radiations to the problems of medicine. This year marks the fiftieth anniversary of the discovery of x rays by Röntgen, an event of outstanding significance both for pure science and medicine, for it provided the physicist with a most powerful weapon of research into the structure of matter, and the doctor with almost a new sense, and diagnostic possibilities of the highest order. Later, the rays were recognized as a lethal agent,

whose proper power and scope against malignant disease are only now being unfolded. The year 1896 saw the discovery of radioactivity, which again has furnished, besides the most profound studies of the structure of matter, a powerful if still largely mysterious agent in the treatment of malignancy. Recently, artificial radioactivity has provided the experimental physiologist with a means of studying metabolic processes, while modern nuclear physics seems destined to influence medicine profoundly as our mastery of atomic techniques develops.

It would be easy to show how the classical lines of development of physical enquiry have been followed in medical radiology, the sequence first of qualitative observation, then of attempts at quantitative measurement, disagreement and final agreement on units of measurement, subsequent discussion of the significance of such units, and the gradual development of mathematical generalization and detailed solution of practical problems. We are here concerned, however, rather with the need for an expanding horizon and the insistence that physics has a wider scope and role in medical thought, research, treatment and education than so far usually accorded to it.

This scope of physics in medicine may, for example, be gauged from an encyclopaedia of medical physics recently published in the United States. Merely to list the headlines would require many pages, and every branch of medicine and surgery is represented.

We think, for example, of the many applications of optical principles in medicine and surgery, ranging from the embodiment of laws of geometrical optics in spectacle-lenses to laryngoscopes, bronchoscopes, cystoscopes, sometimes of

real beauty of design and adaptation. Coupled with the cine-camera, the bronchoscope enables a film to be made during the removal of an obstruction in a bronchus, and the observer is given a veritable conducted tour around the lung. Body cavities have become "accessible" in a new sense. The influence of the rather more subtle laws of physical optics may be found in instruments for measuring the average diameters of blood cells by the haloes they cause around a source of light, instruments descended directly from the "eriometer," invented by Thomas Young for measuring the diameters of fine hairs, at the time when this physician-physicist was laying the foundations of the experimental proofs of the wave theory of light. We might recall the rather obvious fact that the optical microscope is a physical weapon, studied and sharpened to a point where this same wave nature of light is itself the chief and impassable barrier to seeing the still invisible, and recognize in the substitution of streams of electric charges for the beam of light in the new electron microscope the next, and perhaps supremely important, contribution physics has to make to the science of microscopy.

We might similarly range through all the branches of physics and quote examples of the fundamental nature of the physicist's contributions, either in technique or in generalizations of wide and abstract character, which transform the nature of the problem. The use of specific electronic devices like the cathode-ray oscillograph with its attendant amplifiers occurs to us immediately. The science of electronics and electron optics has contributed and will contribute to many of the problems of neurophysiology. It may be noted in passing that "magnetism" seems a slightly disreputable word in medicine, which is unfortunate as it appears that a study of the magnetic properties, magnetic susceptibility for example, of body fluids or tissues, might well yield both useful and interesting information. The study of sound and of modern radio-frequency techniques has resulted in great advances in

applications of acoustics, a subject once more intimately associated with Thomas Young. We think, too, of the possible applications of high-frequency radio science, now making available, both directly and indirectly, power of hitherto undreamed amount at wavelengths of a few centimetres, and applicable to the heating of the human body.

No physicist turning over the pages of an anatomy textbook can fail to see before him fascinating problems in mechanics and the strengths of materials, yet how little we know of the mechanics of fractures or of the instantaneous stresses and strains when the human frame suffers some sudden impact or gradually changing pressure.

It would be, however, tedious and little to the point to attempt to enumerate the various direct or indirect effects which physical techniques have had on medicine, for no list can be complete and the influence is sufficiently obvious.

History of Medical Physics

It would be a fascinating task to trace the history of the connection between physics and medicine. The interaction might perhaps be seen as twofold, the two eternal aspects of scientific progress, on the one hand the gradual development of specific techniques and on the other the grasping of great generalizations, which transform the picture of the world and so of man's supposed place in it and the significance of his needs.

Most frequently the repercussions of physical discoveries are incidental and not at all in the mind of the discoverer. Röntgen may have been gratified at the medical utility of x rays, but certainly no such application was in his mind. This consideration should be kept continually in view in the development of medical research programmes, where the widest possible latitude is necessary. The point is rather the importance of the closest correlation between pure science and medical practice, and the necessity for organization to secure the most rapid and efficient development of scientific discoveries of medical importance.

If it appears that medicine has a debt to physics, there must be at least some corresponding recognition of the contributions made to the fundamental sciences of those whose primary education has been medical. Certainly we cannot claim that the physicist interested in medical problems is a new phenomenon or that medical men have not shown the greatest interest in the use of physical techniques. The significant development of the present day

is rather the emergence of a group of physicists employed solely in the study and control of physical agents in their applications to medicine, and in the recognition that the physicist is now an indispensable member of any team of specialists using x rays or radium in the treatment of malignant disease, and generally in the therapeutic use of ionizing radiations. In this development Britain has played a notable part, and it is probably true to say that the importance of the physical aspects of medical radiology are as well recognized here as anywhere in the world.

It is to be hoped that similar development of physical medicine may occur in the near future, for the crying need in this branch of medicine is quantitative information, a great deal of which can be obtained only by exact physical experiment. It is a curious thing that the use of heat, one of the oldest medicaments, is from the physical point of view almost entirely unscientific, and that only recently have measurements in absolute units been linked to clinical practice.

It is natural that we find the medical man, a member of one of the few educated sections of the community, among the first to make a contribution to "pure" physics. As late as 1600 we have Gilbert of Colchester, physician to Queen Elizabeth, becoming the father of electrical science, or Borelli seeing in the movements of man and animals applications of the laws of levers. Even in the beginnings of the modern epoch we find many physicians and surgeons contributing vitally to pure physics.

Thomas Young perhaps stands out as the physician who, in the early years of the nineteenth century, did most to transform physics into its present shape. Mayer, the tragic German physician, so stoutly championed by Tyndall as one of the discoverers of the great generalization of Conservation of Energy, on the basis, be it noted, of observations of the blood of the Javanese, is a notable medical contributor to physics. Tyndall himself, through his researches in the domain of radiant energy, as well as his intervention in the controversies around spontaneous generation and the bacterial origin of disease, is one of the greatest "medical physicists" of the nineteenth century. Again, physics in medicine certainly found one of its most able exponents in Helmholtz, whose mathematical and experimental ability transformed the science of acoustics, while earlier in the century a German physicist, Ritter, seems to have been the discoverer of ultra-violet radiation, though hotly followed by Wollaston, another medical physicist.

So from the medical student, Galileo, interested in the swinging of a lamp as a time-keeper to his pulse, to Lawrence and his giant cyclotron on the hilltop in California, technical advances in physics have been linked with physics.

As we have already indicated, physics may influence medicine very profoundly by its general conceptions of the Universe as well as by its detailed techniques. The "recent advances" of science are bound to excite the more progressive and impatient medical men of each generation. Again, any adequate account of these relationships is a task for the medical historian, but it is tempting to stray a little and recall the influence of the Newtonian philosophy on the medical practitioner of the early eighteenth century. Newton contributed directly to, and indeed in one sense founded, the science of radiology with his studies of the visible solar spectrum. In radiation physics his influence is obvious, and no one reading, for example, Herschel's description of the experiments following his discovery of infra-red radiation in the year 1800, could fail to note the similarity of the train of thought and experiments with those in Newton's *Opticks*, published about a hundred years earlier. Newton, however, influenced medical thought very profoundly in many other ways, as for example, by his "mechanical" explanation of the Universe, which gripped the imagination of his contemporaries. It is interesting to recall that in 1702 one of the most remarkable physicians of the early eighteenth century, Richard Mead, published *A mechanical account of poisons*, complaining a little that "to unravel the Springs of the several Motions upon which such Appearances do depend, and Trace up all the Symptoms to first Causes, requires some Art as well as Labour." Let Mead speak for himself in his preface:

"My Design in thinking of these Matters was, to try how far I could carry Mechanical Consideration in Accounting for those surprising Changes which Poisons make in an Animal Body, concluding (as I think fairly) that if so abstruse Phaenomena as these did come under the known Laws of Motion, it might very well be taken for granted, that the more obvious Appearances in

the same Fabrick are owing to such Causes as are within the Reach of Geometrical Reasoning "

Again,

"It is very evident, that all other Methods of improving Medicine have been found Ineffectual, by the Stand It has been at these Three or Four Thousand Years, and that since of late Mathematicians have set Themselves to the Study of It, Men do already begin to Talk so Intelligibly and Comprehensibly, even about abstruse Matters, that it may be hoped in a short Time, if Those who are Designed for this Profession, are early, while their Minds and Bodies are Patient of Labour and Toil, Initiated in the Knowledge of Numbers and Geometry, that Mathematical Learning will be the Distinguishing Mark of a Physician from a Quack, and that He who wants this necessary Qualification will be as Ridiculous as One without Greek or Latin."

So much for those who feel that even if Philosophy and Physic can agree, Mathematics and Physic cannot. It seems that mathematics had already invaded medicine, though we might even now be a little shy at claiming such prerogatives for it.

It will doubtless be equally interesting to look back in the year 2200 A.D. and see the influence that the electrical theory of matter, developed during the first few years of the twentieth century, had upon medicine.

Physics in Radiotherapy

Advancing techniques in physics applied to medicine bring problems of organization and human relationships, and it is perhaps interesting to illustrate some of these problems of daily collaboration of physicist and doctor from the field of medical radiology, the only one in which the writer could claim first-hand knowledge. In radiation therapy the closest collaboration between radiologist and physicist is now recognized to be essential, yet even to most non-medical physicists the problems appear strange and bewildering, and it is scarcely surprising that medical radiologists find increasing difficulty in following the detailed mathematical and physical studies of their techniques.

We may take the view that the medical man has so many problems of his own that it is quite impossible and undesirable for him to attempt to follow these details, and similarly the physicist may find incomprehensible what is to the radiologist the most elementary anatomy and pathology. Unless the medical radiologist understands something at least of the power and limitation of the physical methods, he will certainly not be able to make the best use of his physical colleagues, who in their turn will be unable to make relevant suggestions of alteration in technique, or criticisms of present procedures, unless at least superficially acquainted with the medical radiologist's mode of speech.

One of the most efficient ways of bringing together these two groups of people with such different training and therefore outlook, lies in the regular attendance of the physicist at radiological clinics, where he may see the difference between a neat diagram of radiation fields and cancer in its anatomical and most "unmathematical" forms. The radiologist on his part will find regular visits to an experimental laboratory stimulating and chastening experiences. A good deal might be done to relieve the situation by a more systematic training of the hospital physicist. Frequently even a change in mathematical approach to a problem will make collaboration much easier. It will be found, for example, in studying radiation-distributions showing the dose at various points in the tissues, that the medical radiologist will visualize results much more clearly if the physicist avoids formal mathematical analysis and substitutes geometrical methods. A formula is anathema, but the shape of an "isodose surface" is almost anatomy. The physicist is apt to think his job is done when he states, let us say, "that for a length of 2.7 cm the dose in a certain plane does not fall below 90 per cent." Such a statement means little to most medical radiologists, but expressed in the form that "the 90 per cent. isodose surface stretches anteriorly from the lower border of the hyoid bone to the upper border of the cricoid cartilage" instantly brings a look of relief and gratitude. This method of approach implies that the hospital physicist should be instructed in elementary anatomy, so as to be able to take a more intelligent interest in the parts of the body he helps to treat, as well as to be able to transmit his hard-won information in a more acceptable form to his medical colleagues. The anatomy taught to him should of necessity be of rather

a special variety, which we might describe as "geometrical anatomy." Size, shape and position are of more importance to him than structure or function, which clearly lie outside his province.

It has usually been thought that too close a reliance on physical methods leads to rigid techniques and standardized dosage, that the individuality of the patient is lost, and that all is subordinated to an inflexible régime. This is a grave error, and the reverse is more nearly true. There can be no doubt that variation of size, condition, and sensitivity from patient to patient is of the utmost importance, but standardization of technique becomes increasingly indefensible as the detailed physical studies provide the necessary information to enable adjustment of technique from patient to patient to be made on a rational basis. Physical studies of sufficient range tend towards flexibility rather than standardization. This is an important lesson for both medical man and physicist to learn, and they are more likely to learn together than separately.

Only the closest personal collaboration of radiologist and physicist, only the daily discussion of common problems, and the realization that the medical man has the final responsibility but the physicist an indispensable interest, can solve the problem of one of the most important applications of science in medicine. The physicist must realize that however fascinating and important his more academic problems, his primary responsibility in this respect is to be useful, while on the part of the medical radiologist we ask for a more enlightened understanding of the importance of the physicist, not only in solving the technical day-to-day problems, but also as a spearhead of the attack on the fundamental biophysical problems of the structure of living material and its interaction with radiation. As new fields of medical physics develop, doubtless similar problems of co-operation will arise, but the principles of co-operative study and education are universal.

Developing Influence of Physics in Biology and Medicine

It is certain that the materials of the living organism are much more complex than any hitherto subjected to physical enquiry, but that advances in knowledge of the structure of these living materials, both normal and pathological, might bring about revolutionary changes in medicine no one could deny. The use of modern physical weapons like the x-ray spectrograph, the electron microscope with its possibilities of electron diffraction, or the radioactive tracers, offers nothing less. A great deal of the knowledge may not at first be new, but both physics and biology seem to have reached a stage where the techniques and perhaps the "ideology" of physics are becoming vital to biological progress. The cyclotron producing its wealth of artificial radioactive products, and the electron microscope lowering the limits of visible size over a critical region covering the viruses and colloidal particles, make possible an attack on the wealth of organization lying between the small molecule and the visible speck of living matter. These and other weapons hold out promise of rich rewards in a field in which hitherto physics has hardly dared to venture. Whether there will develop a reasonably well-defined science of biophysics analogous to biochemistry it is difficult to foretell. Physics is such a vigorous parent that its lusty children tend to early maturity and independence.

It will not be easy to combine the distinctive features of physics and biology. The conceptions of physics tend towards the static and universal, those of biology towards the dynamic and individual. The physicist learns to deal with effects accomplished and finished with fairly clear comprehension of the chain of events between. The study of living organisms necessitates intrusion into a delicately-poised working mechanism which may react in unsuspected and disconcerting ways. There is apt to be a great gap of ignorance between the original stimulus and the resulting effect, with a consequent belief that the mechanism is much simpler and more amenable to mathematical analysis than is in fact the case. The physicist is prepared to admit variability, but has a feeling that proper statistical methods will lead to unerring conclusions. The biological experimenter (and good clinician) has to make many inspired guesses on most insufficient evidence, and sometimes needs a good deal of convincing as to its inadequacy.

Again the only solution seems to be the closest possible collaboration between experimental biologists, cytologists, biochemists and many others with the physicist, each knowing

enough of the other aspects to visualize the outline of the picture even if the sketch is a little misty

These considerations inevitably raise the question of education. It is an unfortunate fact that most physicists learn extremely little or no biology and conversely that the biologist is usually quite innocent of physics and has an alleged dislike of mathematics. It is most important that opportunities be available for members of both groups to be educated in the two fields. The medical undergraduate, again, presents special problems in this respect, for physics will not be applied in medical practice and so make its proper contribution to medicine unless the doctor of to-morrow has at least some grasp of its scope and potentialities. This is not easy, for the truth is that the fundamentals of physics are often most clearly exemplified with simple non-medical examples, while the branches of physics which are of most direct application in medicine are complex, difficult and often regarded as "unsuitable for children."

Moreover, those teaching physics in the ordinary way have little if any contact with the medical profession and courses are better adapted to the needs of engineers. There can be no doubt that a medical school in the closest possible contact with a large general hospital is the best training ground in medical physics, for even at the most elementary stage it is

very doubtful if the teaching of physics in medicine can be adequately dealt with away from the hospital and patient. Certainly here will occur the best opportunity of making physics a real part of medical education, particularly if the courses are constructed so as to bring vividly and continuously before the mind of the student examples of the applications of physical principles and instruments in daily practice. Without such education it seems improbable that the applications of physics to medicine will be made as rapidly or as completely as desirable.

To sum up then, physics seems destined to assume an increasing importance in medicine, by the introduction both of specific techniques and of general ideas. Its influence has already a fascinating historical background, but the interest at the moment lies rather in the organization and training of physicists devoted solely to discovery and application in medicine. There arise many questions of education and co-operation for both medical man and physicist, and these problems can best be solved by the development of mutual understanding while working together. It seems that we must provide education in both the biological and physical sciences to the hospital physicist of the future, for the developments of biophysics are likely to play an increasing part in medical practice.

BIOPHYSICAL FACTORS IN DRUG ACTION

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The rapid advances which have been made within the past few years in our knowledge of tissue ultrastructure and cell chemistry have introduced new perspectives into the possibilities of a better understanding of the various modes of drug action by closer collaboration between the biologist and the chemist. Perhaps one of our chief difficulties in seeking a rational explanation of the biological activities of drugs in terms of simple physicochemical or biophysical factors is the apparent simplicity of the relationships which may readily be deduced by analogy with artificial model systems. The justification for the use of such models has frequently been based on the assumption that the living system is so complex that the gross properties of a particular structure are often embodied in a simplified reconstructed system.

But the physiologist is now inclined to enquire a little further into the intermediary factors which influence the production of a biological response to a drug. The morphologist is becoming increasingly interested in the dynamic significance of the structures he examines, and he is better acquainted with the uses of the ultra-violet and electron microscopes in detecting structures which cannot be resolved with the ordinary light microscope. Moreover he is able to interpret the molecular arrangements in these structures with the polarization microscope and the methods of x-ray diffraction analysis.

The Analytical Approach to the Study of Drug Action

The aim of the biochemist has primarily been the isolation and analysis of the purified components of the living cell, and considerable information is now available concerning the structural components, which are essentially lipids and proteins, and the vital enzyme-systems which are intimately associated with these components. In this connection, the physical chemist has been able to offer valuable co-operation, for the organization of living matter frequently takes the form of discrete cellular fabrics or membranes, and, apart from the permeability of such membranes, the uptake of a drug is also influenced by the asymmetrical forces resident at their surfaces of separation. Schulman & Rideal (1937) have shown how it is possible to study the nature of the interactions of drugs with the biological components of membranes by means of the Adam-Langmuir trough. Lipids and proteins can be spread on suitable substrates as two-dimensional films, or monolayers consisting of a single layer of molecules. The changes in the physical state, surface pressure, and surface potential of the monolayers gives an

accurate measure of the associating forces between the biological components and the drugs which are introduced into the underlying substrates.

The "Receptor Theory"

Yet despite these ordered advances in what we might term the analytical approach to the nature of drug action, the bulk of existing pharmacological data can be interpreted only by assuming that drugs combine with hypothetical "receptors" in the living organism to produce similar or antagonistic responses. When this occurs it is supposed that the drugs compete for the same receptors in the surface or tissue which is the site of drug action. For example, the bacteriostatic action of sulphonamide drugs is neutralized by the presence of *p*-aminobenzoic acid, an essential metabolite which is utilized by the bacteria. Woods (1940) has advanced the view that the antsulphonamide activity of *p*-aminobenzoic acid is due to the similarity in structure between the drugs and the metabolite, and that owing to this similarity there is a displacement of metabolite from the bacterial enzyme-receptors by the competitive action of the drug. This reduction in available substrate results in an inhibition of bacterial growth.

The "Lipoid Theory" of Narcotic Action

It is less easy to apply the structural relationships of the receptor theory to the mode of action of depressants or narcotics, where activity appears to depend mainly on the physical properties of the drug molecules rather than on special molecular configurations. Here the drugs have a characteristic reversible action. The numerous relationships between the intensity of a depressant action and the changes in the physical properties of narcotics in homologous series of drugs suggest that there is a physical equilibrium between the drug and some component of the living cell which is narcotic-sensitive. If we assume that narcotic action depends on the uptake of the drug by the cell lipids, we can collect a great deal of experimental evidence which supports the coincidence between narcotic action and simple drug-distribution in model systems containing a mixture of oil and water. This relationship forms the basis of the well known "lipoid theory" of narcosis which was advanced towards the close of the last century by Overton (1895, 1896, 1899, 1901) and Meyer (1899). A later generalization by Traube (1904, 1908, 1924) seeks to correlate narcotic action with the adsorption of drugs at cell surfaces or interfaces. Thus "adsorption

theory" depends on the parallelism between narcotic activity and the surface activity of drugs, and it is supposed that the cell lipids are not necessarily the dominant biological substrates or receptors involved in drug uptake

The literature abounds with numerous discussions and criticisms of the Overton-Meyer and Traube concepts. These principles have the outstanding merit of simplicity, and their attraction rests in the abundant evidence that has since accumulated and which lends added support to either theory. An adequate survey of the extensions and modifications of these early generalizations is beyond the scope of the present article, and many comprehensive reviews on the subject are already in existence. But the central problem is to elucidate the mechanism by means of which we can relate narcosis with the depression of the oxidative events of the living cell and also with the association of the drugs with the structural fabric of the cell. We can demonstrate the inhibition of enzymic activity in isolated enzyme systems. We can also detect changes in the molecular orientations of the structural fabrics which form the natural environment of these enzyme-systems but we have been quite unable so far to link these changes in the living system.

Reconciliation of "Rival" Theories

In view of the uncertainty which exists as to the nature of the drug receptors, it may be more constructive at this stage to assume that the "rival" theories which have been proposed from time to time are not necessarily divergent, but are rather expressions of experimentally-observed regularities in the relationships of drugs with particular systems. The justification for this assumption will become apparent when we search for common physico-chemical factors in some of the diverse structural arrangements in membrane organization which are consistent with pharmacological action, and it will be of interest to notice that the anomalous systems often provide more information than those which show more regular coincidence with simple model systems.

The early work of Overton stressed the importance of the lipids in cell organization and membrane permeability, and the parallelism between the uptake of substances by cells and differential oil-water solubility indicated the preponderance of fatty material in the cell membrane. More recently Osterhout and co-workers (Osterhout, 1937) have studied the permeability of homogeneous artificial membranes consisting of organic solvents, such as guaiacol, and have related the passage of substances through such oil films with the permeability of the protoplasmic surfaces of large multinucleate plant cells, such as *Valonia*, *Halicystis*, and *Nitella*. In these systems the cell membrane appears to behave as an oily liquid of low dielectric constant. Collander (Collander, 1937, Collander & Bärflund, 1933) was in general agreement with the view that the penetration of non-electrolytes through the plasma membrane takes place through the membrane lipids, but he found that small molecules penetrate into the cells of the alga *Chara fragilis* more rapidly than would be expected from considerations of oil solubility alone. He concluded that the cell membrane acts as a molecular sieve in which the specialized channels become a dominant factor in drug access when the molecular size of the penetrating molecules decreases to a critical value. Nathansohn (1904) was similarly led to conclude that the cell membrane is heterogeneous, but his concept differed from that of Collander in assuming that the specially-differentiated patches are much larger than molecular sieves, and that the penetration of substances depends on their chemical properties rather than on their molecular size. If we accept the view that the cell membrane is heterogeneous and consists of a mosaic arrangement of relatively hydrated patches distributed in a lipophilic framework, we must also suppose that interfaces exist in the membrane structure, which may, however, approximate to a homogeneous lipid layer in certain types of cells. In this way some measure of agreement is found which relates the Overton-Meyer and Traube principles in terms of structural membrane relationships rather than the relationships which exist in model systems.

Investigations on the Erythrocyte Envelope

The erythrocyte has been the favoured object of much investigation. Despite the convergent attack which has been made on the nature of the structural organization of the erythrocyte envelope, a considerable degree of uncertainty still exists as to its precise structure. Here, also,

the biological complexities in the system are so marked that many new concepts of cell structure have been based on analogy with simple models. For example, by means of the analytical leptoscope Waugh & Schmitt (1940) have estimated that the total thickness of the erythrocyte envelope is about 200 Å of which up to 100 Å may consist of lipid. This instrument has only recently been developed, and the essential principle involved consists in the comparison of the relative intensities of light reflected from the cells and built-up step films of barium stearate of known thickness deposited on a similar substrate to that used for the erythrocytes, which are examined in the form of the dried haemolyzed "ghosts".

Gorter & Grendel (1925) reported that the fat-soluble lipid is sufficient to form a bimolecular layer, 50 Å in thickness, covering the surface of the envelope. Danielli & Davson (1934) and Danielli & Harvey (1935) have proposed a more stable form of membrane which consists of a lipid layer several molecules in thickness stabilized by the adsorption of protein on the internal and external surfaces which are in contact with the more aqueous environment. It cannot be denied that this "paucimolecular theory" (Davson & Danielli, 1943), which is a modification of Overton's concept of a homogeneous lipid layer, serves to rationalize a large body of existing permeability data.

But rather critical evidence has been presented recently by Parpart & Dziemian (1940) which suggests that a considerable proportion of the lipids in the erythrocyte envelope is firmly bound to the structural fabric of the ghost in the form of fat-insoluble lipo-protein "complexes". The molecular ratio of the fat-soluble fractions, comprising the phospholipids, cephalin and lecithin, and the sterol, cholesterol, is more related to permeability than the total lipid contents of the erythrocytes in different mammals. The cephalin fraction is relatively uniform in the different cells, but there is a much greater divergence between the molecular ratios of lecithin and cholesterol. These results have some bearing on the structural features of the envelope, for the permeability to fat-soluble substances shows little variation in the species examined, but a higher proportion of lecithin and cholesterol is present in the cells which are more permeable to lipid-insoluble substances. It would appear that the cephalin has a structural role in the organization of the erythrocyte membrane, while lecithin and cholesterol are involved in the more labile diffusion processes. In support of this we may cite the evidence offered by Chargaff and co-workers (Chargaff & Ziff, 1939, Chargaff, Ziff & Hogg, 1939, Chargaff, Ziff & Rittenburg, 1941, 1942), who found that cephalin forms a salt-like lipo-protein with salmine, which is a basic protein, over a pH range of 2-11, lecithin forms an analogous complex only at pH 10-11. The complex formed between cephalin and salmine has rubber-like physical properties. The dried precipitates swell in water and organic solvents, and they may be recrystallized from ethyl alcohol. Other basic proteins, such as histone, also form complexes.

X-ray Diffraction Analysis

From x-ray diffraction analysis of such complexes, Schmitt & Palmer (1940), in collaboration with Chargaff, assumed the existence of a single layer of protein between each bimolecular double layer of cephalin. According to Schmitt & Palmer the positive polar groups of the extended protein molecules are attached to the negative polar groups of the cephalin molecules on both sides of the protein, and this association results in a decrease in the solvation or hydration of the system. Analogous bimolecular lipid leaflets were detected in emulsions prepared from mixed brain lipids, but the diffraction spacings between the leaflets are much larger than those which occur in the dried lipo-protein complexes. This shows that even in highly solvated systems, the lipid molecules retain their relative orientation to the interlayer aqueous phase. The spacing between the lipid layers in the mixed lipid emulsions is greatly reduced by the presence of divalent cations such as calcium, and this may be related to the conduction of the nerve impulse, for Scott (1940) has reported that the bulk of the calcium in a nerve fibre is located in the myelin sheath.

Boehm (1933), and Handovsky (1933) have described the results of x-ray diffraction analysis on surviving nerves. The association of narcotics with the lipids results in a dispersant action on the packing or orientation of the layers, which become wider and more diffuse. Using similar methods, supplemented by birefringence studies in polarized light,

Reynolds, Corrigan & Hayden (1940) were led to believe that orientated lipid associations occur in the human brain, but the degree of orientation varies and is apparently more marked in nerve trunks than in white matter

The Pattern of Lipid-Protein-Enzyme Relationship

These diverse observations stress the close relationship between the lipids and proteins in organized tissues. We may imagine that the lipids exert a protective action on the protein structural components of membranes. Baker, Harrison, Miller & Wexler (1941) have found that the action of synthetic detergents on bacteria is inhibited by the presence of phospholipids, and it is supposed that the denaturation of the proteins of the bacterial membrane is prevented by the lipids. Perhaps a similar protective action may account for the resistance of the cell membrane or ghost to the digestive action of pepsin and trypsin, but Ballentine & Parpart (1940) point out that this may depend on the resistant nature of the protein itself, and have suggested that the structural proteins of the erythrocytes are sclero-proteins, possibly of the albuminoid type.

It is permissible to conclude from these examples that, although we have not yet obtained a coherent pattern of the way in which lipids, proteins and enzymes are organized in living systems, the shape of this pattern is gradually being resolved. The biologist holds the initiative in this respect, for, as he extends the range of his biological systems and his technical resources for examining these systems, he can select model systems to assist in the elucidations of the complexities of membrane structure, instead of selecting his biological systems to elucidate complexities in model systems which are of uncertain biological significance. What may we profitably look for when we encounter a natural membrane which we have not examined? We can visualize a structural framework or fabric composed of a relatively resistant lipo-protein complex in which the components swell in fat-solvents or water but are not readily dissolved in these media. Incorporated functionally in this framework are labile lipids and proteins or lipo-proteins, and possibly enzymes which can be more readily displaced or removed from the membrane lattice. The membrane is heterogeneous or mosaic in structure, but the preponderance of lipids may confer upon the membrane the properties of a homogeneous oil layer. Moreover the membrane may have a lamellar structure, which possesses peculiar significance according to the particular physiological function of the membrane.

Insect Cuticle as Test Material

The author (Hurst, 1940, 1943a, 1943b) has found that the study of the uptake of drugs by insects is facilitated by the fact that the cuticle can be readily removed from the insect and studied as a separate physico-chemical system. The insect cuticle consists of an outer lipoidal layer which covers a much thicker inner more hydrophilic layer. The outer layer, which is only a few μ in thickness contains lipids incorporated in a lipo-protein framework. A proportion of the lipids can be removed by the action of fat-solvents. This outer layer, or epicuticle, confers on the cuticle framework its physiological function as a water-impermeable membrane. The inner layer, or endocuticle, may be more than 100 μ in thickness, and consists of hydrated protein closely associated with chitin (Fraenkell & Rudall, 1940) together with a smaller proportion of lipids. This layer serves a mechanical supporting or exoskeletal function in relation to the internal tissues and body-fluids. The cuticle has a pronounced lamellar structure, and the positive form birefringence indicates the presence of orientated lipids in the lamellae, while the extension of the molecules of protein parallel to the cuticle surface is supported by the x-ray diffraction studies of Fraenkel & Rudall (1940), and by the fact that the cuticle can be mechanically separated into component layers.

Effects of Mixed Drug Systems on Insect Cuticle

The soft cuticles of blowfly larvae, or "maggots", are very suitable for experimental manipulation, and they can be attached to small tubes in the form of osmometers. Some very interesting results have been obtained from the study of mixed drug systems. Owing to the high resistance of the cuticle, drugs may be applied to the insect at concentrations which would be rapidly toxic to less resistant organisms.

When an aqueous solution (10 %) of ethyl alcohol is injected into the blood of the blowfly larva, *Calliphora erythrocephala*, the insect is rapidly paralysed, but will remain active in pure alcohol for more than an hour when this is applied externally. It is clear that the alcohol cannot penetrate through the cuticle into the tissues of the insect. If the alcohol is now diluted (1:1) with a fat-solvent, such as kerosene, which is by itself non-toxic, the insect is killed in less than a minute, starts to swell owing to the rapid penetration of alcohol into the tissues, and bursts explosively in about 4 minutes, during which time the body-weight has increased by some 50 % (Fig 1a). If the insect is transferred from the alcohol-kerosene mixture to pure alcohol when the body-weight has

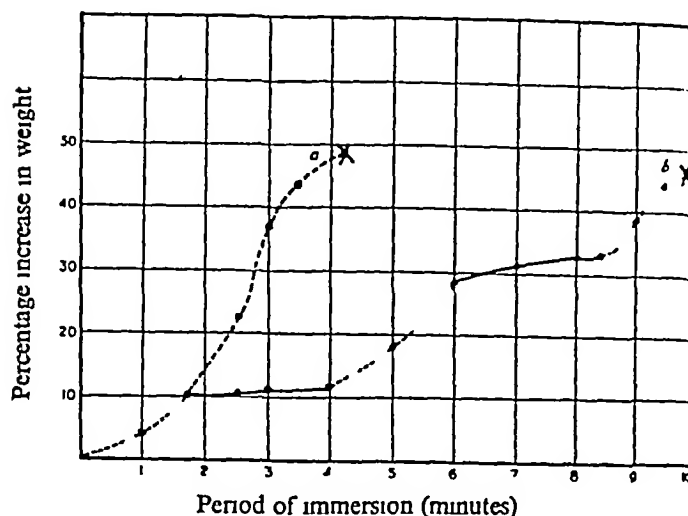


FIG 1 UPTAKE OF ETHYL ALCOHOL BY BLOWFLY LARVAE (*Calliphora erythrocephala*)

- a Continuous immersion in alcohol + kerosene mixture.
- b Alternate immersion in alcohol + kerosene mixture and pure alcohol.
- x Bursting point of insects
- alcohol + kerosene.
- alcohol.

increased by 10 %, the rate of swelling slows down and stops, but increases again rapidly when the insect is returned to the mixture (Fig 1b). These effects can be repeated in smaller increments and are not dependent on vital transfer processes, for they can be reproduced with the isolated cuticle attached to a small osmometer filled with water.

The penetration of the alcohol through the cuticle is clearly dependent on the presence of kerosene in the cuticle framework. This must be a very labile association, as the kerosene is readily eluted from the cuticle when the insect is transferred from the mixture into the pure alcohol. The penetration of alcohol which is induced by kerosene is accompanied by a simultaneous increase in the exosmosis of water from the cuticle. This can be observed in the cloudy swirling zone near the surface of the cuticle indicating that kerosene is thrown out of solution in this region. The insect is not dehydrated when immersed in pure alcohol.

Similar results can be obtained with methyl or propyl alcohol, and with fat-solvents such as ether, benzene, or chloroform instead of kerosene. The synergistic action is also shown in mixtures which contain structurally-related components, such as ethyl and octyl alcohol. Here, apart from its own toxicity, the octyl alcohol increases the permeability of the cuticle to ethyl alcohol, resulting in a progressive swelling of the insect which does not occur in octyl alcohol alone.

The problem which arises is to decide how fat-solvents, which are only slightly soluble in water, increase the permeability of the cuticle to water-soluble fat-solvents and also to water. Experiments with isolated layers of the cuticles attached to osmometers show that the site of the increase in cuticle permeability is in the outer lipophilic epicuticle. The inner thicker endocuticle layer is very permeable to water, and exosmosis of water takes place very rapidly when this layer is in contact with ethyl alcohol or with alcohol-kerosene mixtures. We are led to consider the possibility that the uptake of kerosene by the epicuticle lipids does not involve only a simple swelling or disorientation of this phase *in situ*, but also a displacement of lipid from the more hydrated protein or lipo-protein components. But the effects of induced penetration of alcohol also occur when the fat-soluble lipid has been removed from the cuticle, so we must study the structural organization of the cuticle for a further clue to the nature

of the spatial relationships of the lipids and proteins in the epicuticle. For this purpose the epicuticle is stained red with acid fuchsin and the underlying endocuticle is counter-stained with iron haematoxylin.

Structure of Insect Cuticle

In a transverse section, through the cuticle of the blowfly larva, *Sarcophaga falcata*, the heavily-stained epicuticle is apparently homogeneous, but in a tangential section the heterogeneous or mosaic structure of this layer can be clearly seen (Figs 2a, b). There is a closely-packed network of

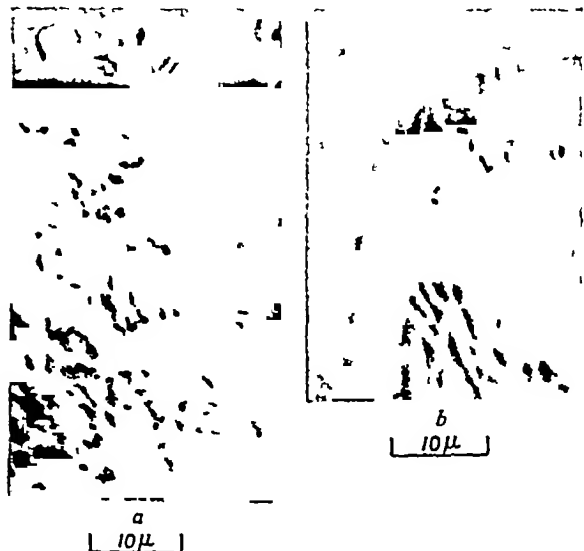


FIG. 2. a Transverse section through cuticle of blowfly larva, *Sarcophaga falcata*, showing densely stained outer epicuticle and portion of inner lamellar endocuticle.

b Tangential section through epicuticle, showing mosaic lipophilic network (dark strands), and transitional zone between epicuticle and endocuticle.

lipophilic aggregates which have a somewhat fibrous appearance and are generally radially disposed across the epicuticle framework. The network is interlaced with more hydrated processes from the underlying endocuticle. Lamellation cannot be seen in the epicuticle although it is marked in the endocuticle. This may be due to the more heavily-staining outer layer, and as both layers are secreted by the same layer of epidermal cells it is probable that a lamellar fabric exists also in the epicuticle. The spacing between the layers is relatively wide in the endocuticle and it is possible that a more minute form of structure may be revealed by x-ray diffraction analysis. If we assume the existence of a microscopic lamellar fabric in the epicuticle, and suppose that the visible mosaic network is incorporated in the membrane, the gross relationships of the structural components become more apparent (Fig. 4a).

Effect of Permeability on "Tanning"

We can explain the action of fat-solvents in increasing the permeability of the cuticle to other fat-solvents such as ethyl alcohol by assuming that the solvents swell the more lipophilic radially-disposed strands of the mosaic network which extends across the epicuticle. But we still have to account for the associated increase in the permeability to water, and this makes it necessary to depart somewhat from the usual classical concepts in which the heterogeneity in a membrane is supposed to consist of pores or channels. Any increase in the permeability of the cuticle to water will probably involve the displacement of protective lipid from the more hydrated protein or lipo-protein structures. But the more hydrated protein or lipo-protein structures will tan as *p*-benzoquinone, the protected protein zones will tan more slowly than those in which access of *p*-benzoquinone is restricted by the competitive action of the lipid for the amino groups of the protein.

As with ethyl alcohol, the access of *p*-benzoquinone through the cuticle takes place more rapidly in kerosene than in alcohol or water, and this can be measured by the darkening in alcohol or water, and this can be measured by the darkening of the cuticle and by the lethal symptoms which are coincident with the first visible signs of a reddish-brown tinge in the cuticle. The tanning action of the quinone monomer is also accompanied by the deposition of the coloured polymerized oxidation products, and these can be observed in optical

sections of the cuticle outer layers. The mosaic structure of the epicuticle in the housefly larva, *Musca domestica*, is now shown up clearly by the differentiation of the tanned zones from the untanned zones where the lipid is more strongly attached to the protein. The extension of the dimensions of the tanned regions which takes place under the progressive action of chloroform- or kerosene sensitization results in a reduction in the more lipophilic zones, corresponding to the mosaic shown in Fig. 2b. We may conclude that the lipid between the discrete aggregates of the mosaic is also more readily displaced from the apparent network in which the lipophilic mosaic is embedded (Fig. 3a, b, c). The fact

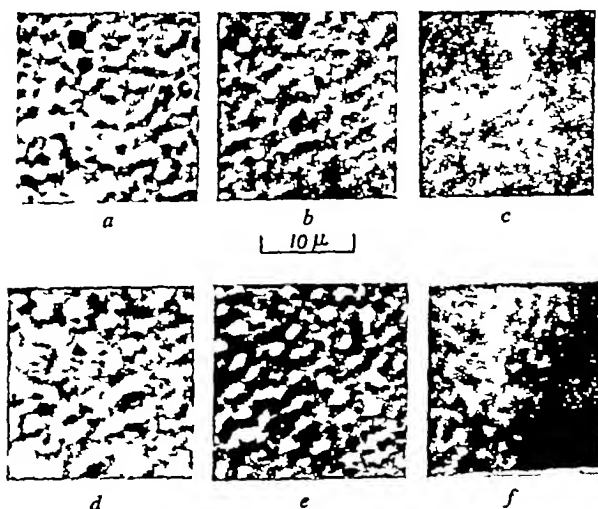


FIG. 3. ARTIFICIAL TANNING AND HARDENING OF INSECT CUTICLE (*Musca domestica*)

a, b, c Optical section of epicuticle layer, showing progressive tanning by *p*-benzoquinone in mosaic network where lipid is displaced by fat-solvent action (dark regions) (NON-ENZYMIC).

d, e, f Similar progressive tanning by catechol (ENZYMIC).

that the whole cuticle becomes eventually deeply tanned and hardened by prolonged treatment with *p*-benzoquinone indicates the general lipo-protein character of the cuticle structure. We may conclude that the spatial changes produced by a fat-solvent or narcotic in the mosaic organization are as shown in Fig. 4a, b. There is a general swelling and increase in phase volume of the lipophilic radially-arranged aggregates, resulting in an increase in the permeability of this phase to fat-solvents which have less lipid-dispersant properties, such as ethyl alcohol. At the same time there is a disorientation and displacement of lipid, probably from the general lamellar fabric of the epicuticle, and this results in an increase in the hydration of the lipid and the protein from which the displacement occurs. In this way the permeability of the cuticle to water and *p*-benzoquinone is increased.

Permeability and Enzyme Activity

Finally, we can now consider the interesting question of the relation of these changes in membrane permeability to the activity of enzymes which are protected by the environmental influence of the membrane framework. A lipid-free gelatine membrane immersed in a *p*-benzoquinone substrate becomes rapidly tanned, but if we now substitute a catechol substrate for the *p*-benzoquinone, tanning of the membrane does not occur. Wagreich & Nelson (1938) have shown that the enzymic oxidation of catechol results in the production of an intermediary *o*-quinone. This quinone has tanning properties similar to those of *p*-benzoquinone, and it is readily produced by the action of an enzyme known as peroxidase which can be extracted from horse-radish roots (Keilin & Mann, 1937). Catechol is very rapidly oxidized in an aqueous substrate containing peroxidase and hydrogen peroxide, and gelatine membranes in this substrate become rapidly tanned by the diffusible *o*-quinone. Similarly we can prepare gelatine membranes which contain peroxidase. These also become tanned when in contact with catechol and hydrogen peroxide, but here the reactive *o*-quinone is formed within the membrane framework. Insect cuticle behaves as a membrane of this type, for it contains an enzyme system which oxidizes catechol very rapidly in the presence of hydrogen peroxide. This enzyme system is involved in the natural hardening of insect cuticle. Both the enzyme and

natural polyphenol substrate are secreted into the cuticle by specialized epidermal cells. The rate of natural tanning is increased by abrading the outer layer of the cuticle and impregnating the abraded layer with a concentrated aqueous horseradish-peroxidase extract. Alternatively, the penetration of catechol into the cuticle is increased by treating the cuticle with a fat-solvent and then immersing the insect in an aqueous catechol substrate containing hydrogen peroxide

bounding membranes of the component cells. Using appropriate substrates, analogous results can be demonstrated with the phenoloxidase systems, catechol oxidase and tyrosinase, which are also present in the cuticle and internal tissues.

These results can be most logically explained by postulating a lipo-protein mosaic structure in the cell membranes of the tissues, in which the availabilities of the enzymes are influenced

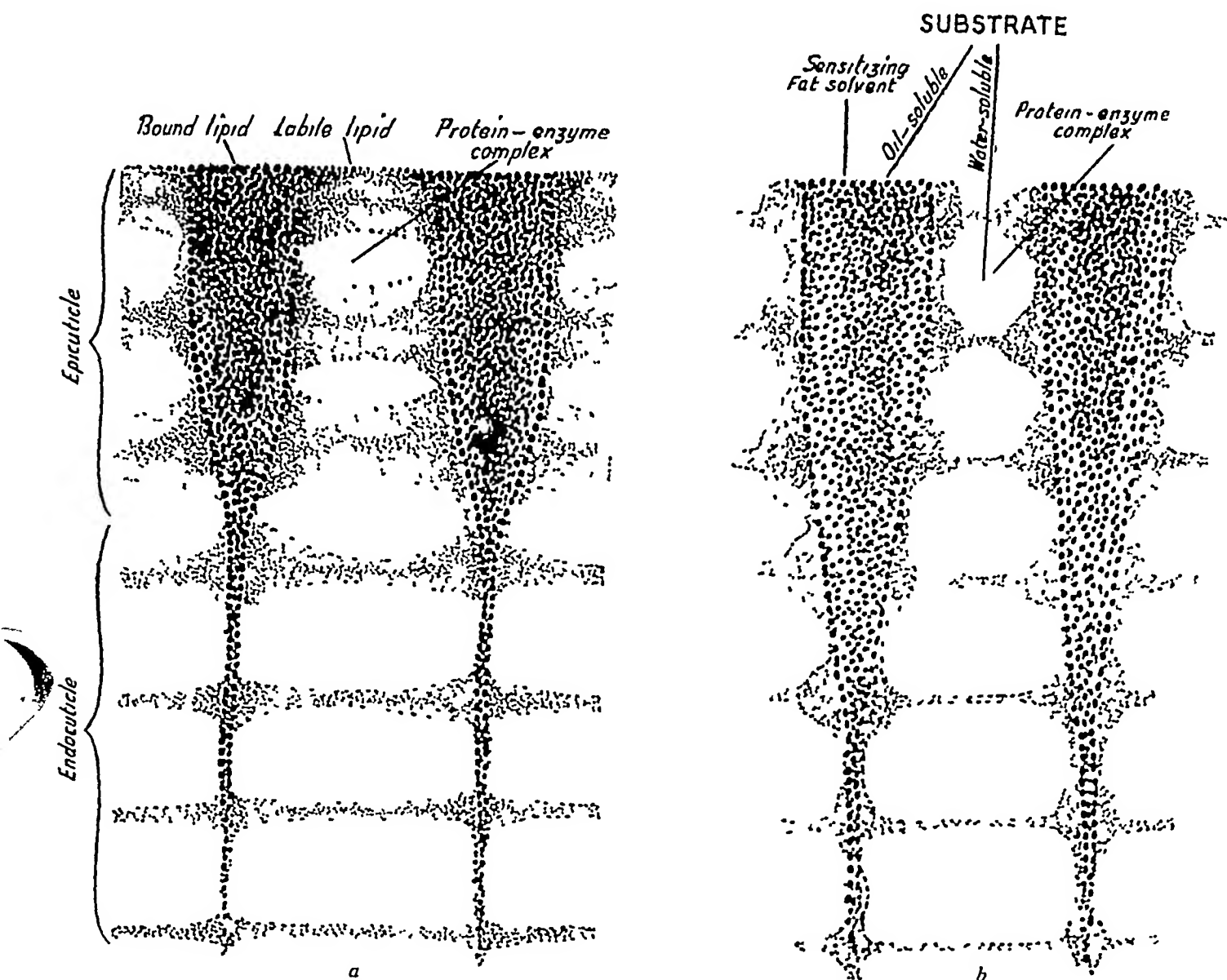


FIG 4 MECHANISM OF SENSITIZING ACTION OF FAT-SOLVENTS ON INSECT CUTICLE

- a* Mosaic arrangement of bound and labile lipid in lipo-protein framework of cuticle of blowfly larvae. A lamellar distribution of labile lipid is shown in the epicuticle and endocuticle
- b* The uptake of a fat-solvent, such as chloroform, results in a swelling of the bound lipid mosaic network. There is a simultaneous displacement of labile lipid, resulting in an increase in cuticle permeability to fat-soluble and water-soluble substances

The catechol is oxidized to the *o*-quinone inside the cuticle framework, but the diffusion of the quinone within the membrane framework does not take place uniformly owing to the mosaic structure, and in this respect the insect cuticle differs from the simpler homogeneous gelatine membrane

But when we examine the pattern of enzymic tanning which has been induced in the cuticle (Fig 3*d, e, f*) we see that it is similar to that induced by the non-enzymic tanning with *p*-benzoquinone (Fig 3*a, b, c*). We note further that there is a general parallelism between the degree of induced enzymic cuticle tanning produced by sensitizing the cuticle with fat-solvents such as hexane, heptane, benzene, ether, or chloroform and the degree of non-enzymic tanning by *p*-benzoquinone induced by the action of these fat-solvents on the protective lipids in the cuticle framework. We conclude that access of catechol to the cuticle enzyme-receptors is similarly influenced by a permeability-factor or by competitive action of protective lipid on the structural protein-enzyme complex

Analogy between Insect Cuticle and Cell Membrane

It may well be argued that the insect cuticle is a highly specialized membrane which has little in common with the more complex and sub-microscopic cell membrane. But when intact isolated insect tissues are treated with a fat-solvent such as chloroform, there is a large increase in tissue-peroxidase activity, suggesting a similar sensitization of the

by the labile lipids present in the structural frameworks. Similar increases in the availability of these enzymes can be induced in the intact insect by two different kinds of physical stimuli: (i) heat, which increases cuticle permeability and phenoloxidase activity in the internal tissues, and (ii) mechanical damage of the cuticle and tissues which exposes the available enzymes. If the posterior segments of an insect such as mealworm larvae (*Tenebrio molitor*) are subjected to the action of (a) chloroform, (b) heat (40–45° C) and (c) mechanical damage by squeezing, the insects first become paralysed, and this stage is followed by a similar local blackening in the posterior segments owing to an increase in the availability of tissue tyrosinase in these regions, a change which is associated with an increase in oxygen uptake.

These results are in accord with Henderson's suggestion that narcosis and oxidative processes are separable phenomena (Henderson, 1930). Although fat-solvent narcotics appear to exert a physical action on the cell lipids, the secondary changes which cause a disturbance in oxidative metabolism may be much more complex. In insects, the increase in tissue-phenoloxidase activity results in the accumulation of reactive *o*-quinones in the blood and tissues. Richter (1934) has shown that these oxidation products act as powerful inhibitors of catechol-oxidase activity, it is likely that they would exert a general toxic action on the vital processes within the insect.

Conclusions

It is doubtful whether this selective environmental influence of the structural tissue components on enzymic activity can be simulated specifically in reconstructed enzyme systems, where we study the nature of the reactions, but not their dynamic aspects in relation to the living system. The so-called "law of homologous series," which expresses the regularity with which pharmacological activity increases with the length of hydrocarbon chain, is possibly due to the close association of the lipids and enzyme-receptors at the site of drug action. The primary role of the structural lipids may be the storage and presentation of drug to the active groups in the enzyme system.

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The characteristic rise and fall in activity as a series of homologous drugs is ascended, for example, with the maximum pressor activity in the aliphatic primary amines, antiseptic activity of the alkyl phenols (Coulthard, Marshall & Pyman, 1930), resorcinols (Leonard, 1924), and bactericidal and fungicidal activities of alkyl derivatives of *o*- and *p*-chlorophenols investigated by Klarman, Shternov & Gates (1934), may simply be due to some optimal association of the drugs with the structural lipids or lipo-proteins which is consistent with maximum access or presentation of the drugs to the associated enzyme-complex. This concept would also explain how the maximum activity in a homologous series of drugs may vary in different tissues and organisms.

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A SURVEY OF THE APPLICATIONS OF ELECTRONICS IN MEDICINE

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Electronics in medicine covers such a large field that in this article only some of the more important and interesting aspects of the subject can be dealt with. There is hardly a branch of medicine which cannot benefit from the application of electronics.

The phenomena with which a physician has to deal—sound, pressure, heat, etc.—can easily be transformed into electrical equivalents which can be amplified by thermionic-valve amplifiers, and graphically recorded. Bio-electric quantities, such as the electrical variations of the heart, lend themselves readily to valve-amplifier technique and registration. The extent of amplification of the signal is governed by the amplification given by the valves in the various stages and is modified by the attenuation which occurs as a result of the relationship of signal frequency to the resistance-capacity values used for coupling. This relationship is the frequency response characteristic of the amplifier.

The amount of useful amplification really depends on the "resolving power" of the amplifier, i.e. the smallest potential change that can be detected, and this in turn is mainly dependent on the working of the first stage of the amplifier. At present we can detect an input change of one microvolt in a circuit of high resistance, like a small nerve trunk, but it is difficult to deal with anything less than this because of fluctuations introduced by the resistors, valves, etc.

Nerve Action-potentials

Nerve fibre is a tissue in which some of the properties of living matter, especially conductivity and excitability, have become developed to an exceptional extent. The electrical stimulus is the common one employed experimentally,

but chemical or mechanical stimuli are also effective. A nerve impulse travelling along a nerve fibre is accompanied by a characteristic electrical change, which is a diphasic potential wave. Once the impulse has been initiated in a nerve, it is "all or none." If a nerve fibre is stimulated electrically, the rate of travel and magnitude are independent of the strength of the stimulus, and depend only on the state of the nerve at the point under consideration. In any particular fibre, stronger stimulation causes only an increase in the frequency of the potential waves. A nerve trunk may contain thousands of fibres of varying types and sizes, and records may show a complex series of transients. In the human body, the waves have a peak potential of about 1.0 mV (which is only a fraction of that developed by the nerve owing to the shunting effect of the inactive adjacent fibres in the nerve trunk) and last about 1.0 millisecond.

The early work on nerve action-potentials was handicapped by the fact that the majority of recording instruments which were sensitive enough for the purpose, for instance, the capillary electrometer and the string galvanometer, required appreciable power to work them, besides suffering from inertia. Pioneer work was done by Adrian (1926), using a capillary electrometer, and Forbes & Thacher (1920) with a string galvanometer. Gasser & Erlanger (1922) used the cathode-ray oscillograph as the recording device. Adrian (1932) in his monograph on *The mechanism of nervous action*, gives a review of the work done in this field to that date.

Wever & Bray (1930) had the courage to connect the auditory nerve with an amplifier and telephone. They found that any sound reaching the ear was reproduced in the telephone, speech could be understood and the speaker

identified by his voice. These nerve action-potentials can be demonstrated visually by means of the cathode-ray oscillograph.

A suitable amplifier for the demonstration of the electrical changes in sensory nerves consists of a four-stage resistance-capacity coupled amplifier employing MH_4 thermionic triode valves. The plate of the first valve is fed through a resistance of 50,000 ohms, 20,000 ohms of which is used for decoupling through a 4 mfd condenser. The second valve is fed through a similar resistance, 10,000 ohms of which is used for decoupling through a 4 mfd condenser. The third valve is fed through a similar resistance, and the decoupling is the same as in the preceding valve. The output valve is fed through a 11,000 ohms resistance, 1,000 ohms of which is employed for decoupling through a 4 mfd condenser. The anode of this stage is fed via a 2 mfd condenser, and the earth line to the Y plates of a cathode-ray oscillograph. The inter-coupling condenser of each stage is 1 mfd, and the grid-bias resistor is 0.25 meg ohms, giving for each stage a time constant of 0.25 seconds.

Various specialized amplifiers and general-purpose biological amplifiers have been developed for this type of work. Other recording devices besides the cathode-ray oscillograph, such as the mirror oscillograph, have been used.

Muscle Action-potentials

The action-potentials of muscle fibres are similar in shape to those of nerve fibre, but are larger and slower.

Wedensky (1883) used the telephone as indicator to study the rate of electrical changes in voluntary muscular contraction. Piper (1912) used the string galvanometer in recording the electromyogram. Adrian & Bronk (1929) demonstrated that the action-potentials from voluntary muscle can be recorded by means of a concentric needle electrode. Denny-Brown & Pennybacker (1938) showed that the recording of action-potentials from voluntary muscle in certain pathological conditions gave useful information concerning the nature and position of the underlying pathological process. Weddell, Feinstein & Pattle (1943) point out that the activity of normally contracting motor units and of fibrillation can be easily distinguished, and it is consequently possible to decide whether a muscle is innervated normally, partially, or not at all. For the exploration of the whole muscle, about six punctures of the needle-electrode may be required, but this is rarely necessary and gives only trifling discomfort. Elliott (1944) made electromyographic studies of tender muscles in sciatica. He demonstrated that the tender spots in the muscles are, as a rule, the seat of a localized increase of irritability and a continuous discharge of action-potentials, which lasts as long as the needle remains in the muscle.

A technique commonly employed in electromyography is to insert a concentric electrode, made of fine wire running through the centre of a fine-gauge hypodermic needle, into the belly of the muscle. The needle's barrel acts as an earthed shield, and the minute wire electrode picks up the electrical activity of units within a radius of 1 mm. The electrical potentials are amplified by a standard amplifier, and records can be observed and photographed on a cathode-ray tube. Weddell, Feinstein & Pattle (1944) employ a special all-mains-operated amplifier. Cathode-ray oscilloscope tracings are used for permanent records, but for practical purposes, however, only the sounds emitted from an output loudspeaker are noted; the detection of small differences in duration and frequency are more easily assessed by auditory than by visual methods.

Chronaxie Meters and Electronic Stimulators

The effectiveness of a stimulus depends, not only on its strength, but also on the time during which it is allowed to flow through the tissues. Chronaxie is defined as the time during which a current, twice as great as the rheobase, must flow through a tissue to set up activity. It is a measure of the excitability of a tissue.

Brian Denny (1944) developed, from the original circuits of Bauwens, an apparatus which aims at providing the means of determining, accurately, the response to electrical stimulation of muscle and nerve and of applying electrical treatment of known character and dosage.

Ritchie (1944) has described a simple variable "square-wave" stimulator for biological work. The instrument uses two standard triode valves to produce impulses inde-

pendently variable in intensity, duration, and frequency over the wide ranges used in the excitation of nerve and muscle.

Electrocardiography

The electrical variations produced by the heart during contraction are distributed through the body, and can be led off from the moist skin surface of such areas as the arms and legs, and recorded.

Kolliker & Müller (1855) showed, by physiological experiments, that an electrical change accompanies the beat of the isolated frog's heart. Waller (1887) demonstrated similar changes occurring in the human heart, when electrodes are applied to the limbs. He used Lippman's capillary electrometer, and his experiments remained of academic interest only. Einthoven (1903) introduced the string galvanometer which made electrocardiography, in its modern form, a clinical science. Some of the disadvantages of the string galvanometer type of electrocardiograph are, the fragility of the string, the necessity of skin-current compensation, and the use of non-polarizable electrodes.

Because of the extremely low voltage generated by the action of the heart, instruments for its measurement in the past have necessarily been extremely sensitive, and the recorders of these have, therefore, been very delicate. The introduction of thermionic-valve amplifiers, and the substitution of robust oscillographs changed all this. The usual form of recorder employed with thermionic-valve amplifiers was the mirror galvanometer of comparatively low sensitivity. Examples of such instruments are the Victor electrocardiograph and the Matthews electrocardiograph.

The Both electrocardiograph works on the thermionic valve amplifier principle, but feeds a small cutting stylus which indents a specially prepared surface. The resultant electrocardiogram is $\frac{1}{10}$ of standard size, and must be viewed through a microscope for direct visual observation. If a permanent standard-record-size electrocardiogram is desired, the original record must be sent to the agents for enlarging.

The ink-writing electrocardiograph uses a valve amplifier and an ink-writing oscillograph. The record is made on inexpensive paper tape. It is immediately visible, and requires no process of developing or fixing. The upper-frequency response of the instrument is limited, due mainly to the friction between the writing pen and the recording paper.

For exact reproduction of the wave-shape of the electrocardiogram, it is essential to use an oscillographic recording element which will respond to the highest-frequency components. Such a device is the cathode-ray oscillograph. The cathode-ray tube is essentially an oscillographic indicator characterized by two striking and valuable properties, first, the almost complete absence of inertia in the recorder, and, secondly, the two-dimensional recording field. The tube, itself, is essentially a complicated thermionic valve. It contains, at one end, an electrode structure, called the "electron gun," and, at the other end, the fluorescent screen. The "electron gun" possesses a filament, a cathode, a grid, and an anode. The electrons emitted by the heated cathode are accelerated by the high positive potential of the anode, and are caused to pass down the length of the tube in the form of a narrow beam. These high-velocity electrons impinge on a fluorescent screen, and there give rise to a spot of light. The direction of motion of the electrons, forming the electron beam, is affected by electric or magnetic fields. At any point between the accelerating system (or "electron gun") and the screen, the beam may be deflected by the electric or magnetic field; the resulting displacement of the spot is a measure of the strength of that field. In the most usual arrangement, the cathode-ray tube is fitted with two pairs of deflecting plates mutually at right-angles, and the deflection of the spot along an axis is closely proportional to the voltage-difference between opposite plates. In the gas-focused type of tube, the combined action of a small amount of gas within the tube, and of the negative grid potential, causes the beam to be focused to a fine spot. A modern high-vacuum type incorporates several refinements. Instead of a simple plate for the anode, two or more cylinders are used; focusing is brought about by electrical optical means. The pair of deflecting plates in the vertical plane are called the Y plates, and those in the horizontal plane are called the X plates. The deflectional sensitivity of the cathode-ray tube is insufficient to produce a record when the heart-

potentials are applied directly to it. A high-gain amplifier is therefore necessary to magnify these potentials sufficiently to give a trace on the screen of the tube. The output of this amplifier is connected to the pair of Y plates, and thus gives a vertical trace. If required, the vertical movements can be photographically recorded on moving film. If it is desired to view the wave-form of the electrical variations of the heart on the screen of the cathode-ray tube, it is necessary for the beam to move slowly across the whole of the screen of the cathode-ray oscilloscope in the horizontal or X axis from left to right. This movement is given by a time-base circuit. For the direct visual observation of the electrocardiogram, the fluorescent-screen material used in the tube is chosen to have a very long after-glow, so that the trace of the spot, when seen in a darkened enclosure, is visible for several seconds after the spot has gone by.

Rijlant (1932), Schmitz (1933) and Matthews (1933) were among the first who adapted the cathode-ray tube to electrocardiography. They used the cathode-ray tube merely as a recording device, and not as an oscilloscope. Robertson (1934) introduced a new electrocardiograph employing the cathode-ray tube as an oscilloscope and fitted with a screen having a long after-glow, which permitted direct visual observation of the electrocardiogram. Brookes-Smith (1935) devised a similar apparatus, but without any device to obviate organ distortion. Asher & Hoecker (1938) mention in their paper that Wilson has adapted the after-glow cathode-ray oscilloscope to electrocardiography.

The cathode-ray tube has been adapted to vectorcardiography by Hollmann & Hollmann (1937), Wilson & Johnston (1938), and others.

Hoff, Kramer, DuBois & Patten (1939) have employed valve-amplifier technique for recording the electrocardiogram of the embryonic heart of the developing chick. Mann & Bernstein (1941), Ward & Kennedy (1942) and others have used electro-encephalographic technique for the registration of the electrical variations of the human foetal heart.

The Phono-electrocardioscope

The phono-electrocardioscope (Donovan, 1943a, 1943b, 1943c, 1944) incorporates a double-beam cathode-ray oscilloscope fitted with a long after-glow screen, which permits the simultaneous and constant viewing of a pair of phenomena such as the phonocardiogram and electrocardiogram at the patient's bedside, whilst the heart-sounds can be heard at the same time through an electrical amplifying stethoscope or a loud-speaker. The double-beam cathode-ray oscilloscope has also many uses in biology and medicine (Donovan, 1943d).

Fig 1 shows a photograph of the apparatus, and Fig 2 a schematic diagram. The heart sounds are picked up by a piezo-electric microphone, which converts them into electrical pulsations. These are amplified by a thermionic-valve

amplifier which has special variable electrical frequency-controls incorporated in it. An electrical stethoscope reconverts the amplified electrical pulsations into sound waves. The phonocardiogram can be directly observed on

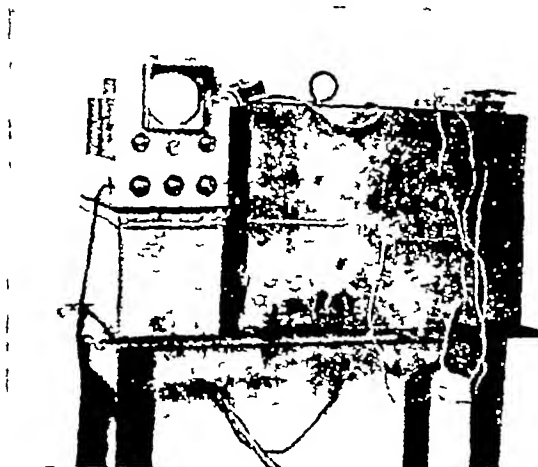


FIG 1 The phono-electrocardioscope.

the long after-glow screen of the double-beam cathode-ray oscilloscope. The electrical variations of the heart can be simultaneously amplified by the second channel, and directly observed as the second trace on the screen.

The following are some of the uses of the phono-electrocardioscope in cardiology

- i Simultaneous direct visual observation of the phonocardiogram and electrocardiogram, plus amplified auscultation
- ii Simultaneous direct visual observation of the phonocardiogram and sphygmogram, plus amplified auscultation.
- iii Simultaneous direct visual observation of the electrocardiogram and pneumocardiogram, plus amplified auscultation
- iv Simultaneous direct visual observation of a logarithmic phonocardiogram, and stethoscopic phonocardiogram, or any one of the foregoing with a linear phonocardiogram, plus amplified auscultation
- v Simultaneous direct visual observation of the phonocardiogram of one area with that of another, plus amplified auscultation
- vi Simultaneous direct visual observation of any pair of electrocardiogram leads, such as leads I and III
- vii Photographic registration.
- viii Murmurs or desired sounds can be accentuated and undesirable ones muted by filter controls

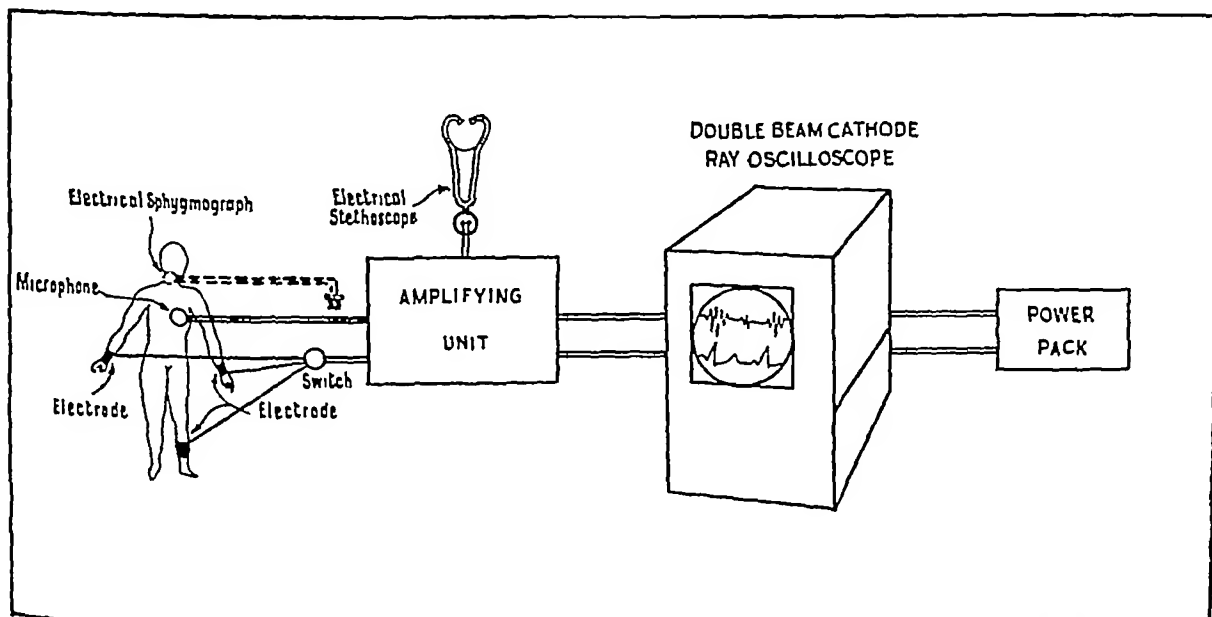


FIG 2 Schematic diagram of the phono-electrocardioscope

Fig 3 shows a peculiarity of the double-beam cathode-ray tube. It will be noted that the bottom logarithmic phonocardiogram is apparently 180 degrees out of phase compared with the similar trace on the top. This can be rectified by

gram, lead II, and a stethoscopic phonocardiogram taken over the mitral area of a case of rheumatic endocarditis.

The loudness of the heart-sounds as heard in the amplifying stethoscope is governed by a tone-compensated gain-control,

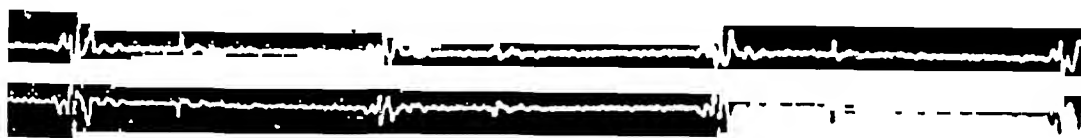


FIG 3 The same apical phonocardiogram has been recorded by both beams on moving film. It will be noted that they are apparently 180° out of phase, and that there is no "fogging." Illustrative tracing taken with the author's phono-electrocardioscope.

reversing the input leads for the bottom trace. The pair of traces have been recorded on moving film, and, despite the long after-glow screen, there is no trace of "fogging." Fig 4 shows a logarithmic phonocardiogram and electro-



FIG 4 Logarithmic apical phonocardiogram. Electrocardiogram, lead II. Recorded on moving film. Illustrative tracing taken with the author's phono-electrocardioscope.

cardiogram, lead II, recorded on moving film. The precaution mentioned above has been adopted and the electrocardiogram shows the right way up.

Fig 5 shows how a pair of traces look on the screen when viewed directly. The top trace is electrocardiogram, lead II,

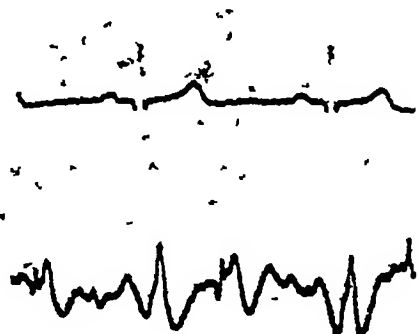


FIG 5 Electrocardiogram, lead II. Electrical jugular pulse tracing. The traverse of the pair of spots was photographed as they appeared for visual observation—opening the shutter at the beginning and closing it at the end of the traverse of the spots. Illustrative tracing taken with the author's phono-electrocardioscope.

and the bottom trace is the jugular-pulse sphygmogram. They have been photographed by focusing a camera on the fluorescent screen of the double-beam cathode-ray oscilloscope, and taking one traverse of the pair of spots as they appear for visual observation—opening the camera shutter at the beginning, and closing it at the end of the traverse of the spots. Fig 6 is similar to Fig 5, but shows electrocardio-

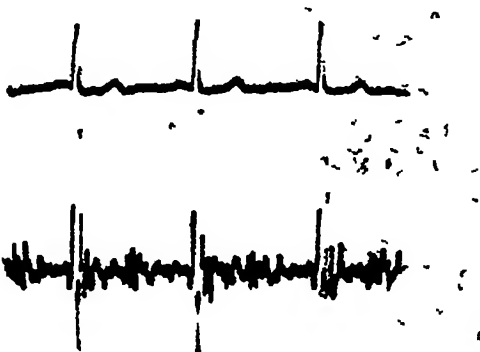


FIG 6 Electrocardiogram, lead II. Apical phonocardiogram of a case of rheumatic mitral endocarditis. The traverse of the pair of spots was photographed as they appeared for visual observation—opening the shutter at the beginning and closing it at the end of the traverse of the spots. Illustrative tracing taken with the author's phono-electrocardioscope.

which helps to correct certain deficiencies in the human ear in which the auditory sensation produced by complex sounds may be decidedly different in character as well as intensity when the stimulating level is increased or decreased. Such a device permits greater latitude in varying the intensity levels at which the heart-sounds are heard.

It is easy to pick up the jugular sphygmogram by shunting the microphone with a 1 mfd condenser. The shunted condenser microphone method is also used for recording the pneumocardiogram. It is an obvious advantage to have an all-electric method of recording these traces.

The phono-electrocardioscope is of value in teaching, research and clinical medicine.

Electroencephalography

The technique of electroencephalography is analogous to that of electrocardiography, viz. amplification and registration of the electrical potentials from the brain as picked up

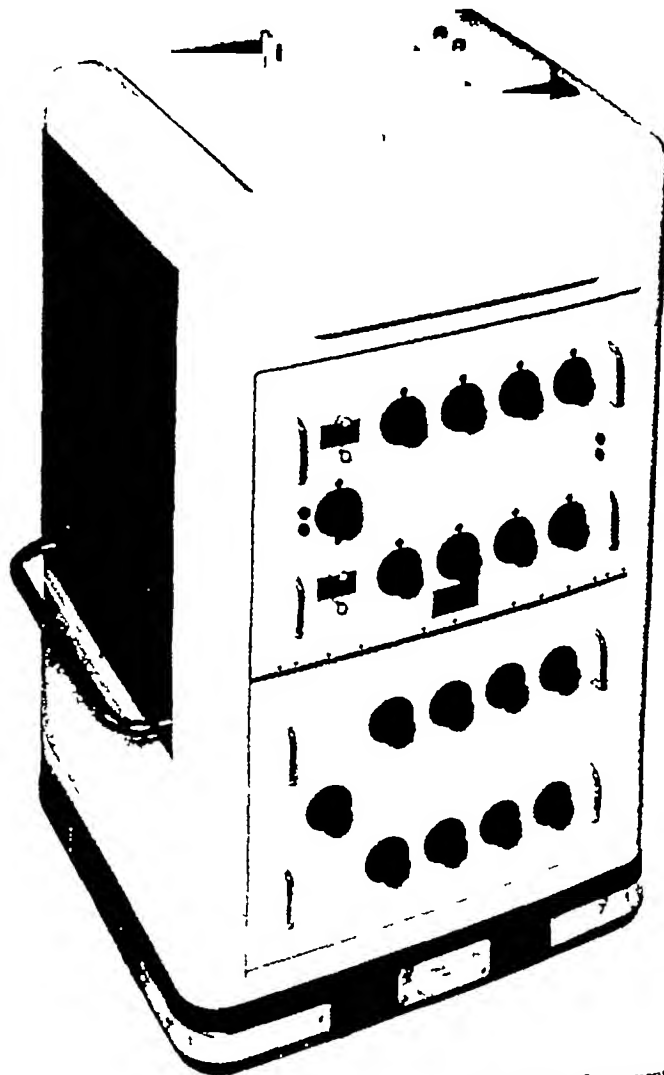


FIG 7 The Marconi encephalograph. (Courtesy of Marconi Instruments, Ltd.)

from the surface of the body. The upper limit of size of the brain potentials as led off from the scalp approaches that of the electrocardiogram, i.e. about 1 mV. Potentials even greater than this are obtained when leads are placed directly on the exposed cortex. Discharges of this magnitude are rare, and only found in abnormal conditions.

The electrical variations generated by the brain fall into certain patterns. The alpha waves, normally present in

most people, have frequencies in the neighbourhood of 10 cycles per second and amplitude of 10–50 microvolts. The beta waves have a frequency of 30–40 cycles per second, but are of lower voltage. Low-frequency waves, below 3 cycles per second, are called delta waves, and are often of larger amplitude than either the alpha or beta waves. The patterns are frequently superimposed. Walter & Dovey (1944) suggest that rhythms at about 6 cycles per second should be termed "theta" rhythms, and that such rhythms are characteristic of the resting, immature or isolated parieto-temporal cortex. Single rounded waves, alternate with sharp spikes, are found during epileptic seizures, sometimes not perceptible through other symptoms. Williams has dealt with the clinical application of electroencephalography in a recent number of the *British Medical Bulletin*.¹

The cathode-ray tube suggests itself as the most convenient form of recording apparatus in electroencephalography, but its use in this field is by no means universal. It is being replaced, for routine work, by the ink-writing recorder. The mirror oscillograph is still used by some workers.

Parr & Walter (1943) describe the technical methods, and give circuit diagrams of amplifiers suitable for electroencephalographic recording. Traugott (1943) discusses electroencephalograph design and publishes the circuit of his amplifier. The Technical Sub-committee of the Electroencephalographic Society has drawn up recommendations for recording apparatus.

The Marconi four-channel electroencephalograph (see Fig. 7), particulars of which, as far as the author is aware, have not yet been published, consists of two double-channel amplifiers, and a four-pen ink-recorder, with variable-speed paper drive. Each pen is actuated by a moving iron armature, the signal-winding being stationary (a permanent-magnet field system is used). Provision is made for the attachment of auxiliary equipment, such as a cathode-ray oscilloscope, or a frequency analyser. Power supply-units for operation from A.C. (alternating current) supply mains are incorporated. The final smoothing of the high-tension supplies is accomplished electromechanically and, where necessary, electronic regulation is also employed to take care of mains voltage-fluctuations. Each amplifier channel has a differential input and uses a common-cathode push-pull circuit throughout. The time constant is controllable in four steps between 1 second and 0.01 second, and the limit of high-frequency response is variable between 15 cycles per second and 4,000 cycles per second. The upper limit of response with ink-recording is 75 cycles per second. The overall sensitivity is such that, at maximum gain, a 20 microvolt peak-peak input produces a 20 mm peak-peak deflection of the recorder. Inputs up to 100 mV peak-peak are accommodated. The amplifier noise with the input short-circuited and earthed does not exceed 2 microvolts root mean square.

Beevers & Furth (1943a, 1943b) devised the encephalophone which converts the electrical-potential changes into sound waves. Basically, this apparatus is a form of heterodyne oscillator, where the brain rhythm varies the frequency of the heterodyne beat note. The "alpha" and "beta" rhythms give characteristic trills, while "delta" waves produce slow sweeps of tone.

Various ways of supplementing primary inspection of the electroencephalogram have been devised, such as that by Grass & Gibbs (1938). Walter (1943) introduced a device to overcome the difficulties of the foregoing method. Briefly, Walter's method is as follows. A series of tuned reeds are energized by the output of the electroencephalograph. These reeds act as frequency splitters, since each is tuned to a frequency in the band to be studied. Each reed is provided with a fine steel contact wire, which dips in and out of a mercury cup when the reed vibrates, but is just out of the mercury when the reed is at rest. A high resistance, a source of E.M.F. (electro-motive force), and a condenser are in series with this mercury reed-contact. The condenser is charged up to a potential which is a function of the total duration of the contact time, and therefore of the amount of energy at the reed-frequency during the specified time. An amplifier is connected to each condenser in turn by a motor-driven rotary switch, and this amplifier works a wide-arc recording pen across the recording paper on which the original electroencephalogram is at the same time being traced. The summation epoch is chosen to be 10 seconds,

so that each 10-second stretch of record has traced over it a histogram of its spectrum. The analysis is performed automatically every 10 seconds. The details of design are fairly intricate and the adjustment is critical.

Electroencephalographic amplifiers can be modified for use in electromyography, cardiography, and as general purpose biological amplifiers.

Sound

An audiometer is an apparatus for the measurement of hearing loss. Many of these devices have been introduced. A popular model of such an instrument comprises a tone source (a thermionic-valve oscillator working on the heterodyne principle) which has a frequency range of 100–10,000 cycles per second continuously variable. The output of the tone source is fed to a high-fidelity moving-coil ear-piece via an attenuator calibrated to read in hearing loss or gain. An auxiliary control automatically corrects the reading for the variation of the threshold of hearing with frequency. A piezo-electric microphone may be switched into circuit to facilitate speaking to a partially deaf person undergoing test. They are valuable in the diagnosis of deafness and the accurate prescription of hearing-aids. Many a physician who prides himself on his skill with his stethoscope would be surprised at his audiogram if he were tested with an audiometer.

Hearing-aids employing modern small piezo-electric microphones, miniature valves and batteries, and compensating tone circuits, can be of great value to the deaf. Tone-compensated and automatic volume-controls have increased the usefulness of these instruments. Lately, there has been a tendency for wireless specialists to "fit" deaf persons with hearing-aids, this is a dangerous practice. One must remember that many deaf persons will not benefit at all by the use of these aids.

There are many types of amplifying stethoscopes working on the thermionic-valve amplifier principle. Instruments have been introduced for the graphic registration of the heart sounds, which incorporate such devices. Olson (1943) introduced a new acoustic stethoscope which transmits all frequencies over the range from 40–4,000 cycles per second without discrimination or appreciable attenuation, whereas an ordinary stethoscope has an effective range of only 200–1,500 cycles per second. There is a marked falling-off in the frequency-response of an orthodox acoustic stethoscope below 200 cycles per second. A filter-control is incorporated in the instrument described by Olson. The arrangement used for comparing the response-characteristics of this stethoscope with others is as follows. Sound vibrations were developed in the human body by means of a subaqueous loudspeaker fed by an audio-amplifier and audio-signal generator. An artificial ear was first held directly against the opposite side of the body to secure a reference characteristic, and different stethoscopes in turn were then introduced between the artificial ear and the body.

The recording and reproduction of sound is of interest to the physician. Such records are of value for teaching and research purposes. Henriques (1937) described an apparatus for recording the heart-sounds on gramophone records. Sound can be recorded on discs, steel wire, and photographic film. It may also be recorded by embossing a track with a needle on film or plain cellophane strip.

Reynolds (1936) has experimented on the problem of synchronizing the electrocardiogram, as recorded by a cathode-ray type electrocardiograph, with a cinematographic film of the heart cycle. The writer suggests that, theoretically, it should be possible to develop this technique so that a cinematographic film of the cardiac cycle could be produced, which has a sound-track of the heart-sounds. If necessary, a simultaneous jugular sphygmogram, phonocardiogram, etc., could also be shown on the film.

Synthetic sound is a term applied to sound produced by methods like those devised by Rudolf Pfenniger who painted by hand the desired wave-forms, afterwards photographing them on to a sound-track for conversion into sound.

Electronic pH Meters

The estimation of the hydrogen-ion concentration of fluids such as the blood in clinical practice is, in the main, confined to the untimeter method. A number of pathological departments and bacteriological research institutions are now using pH meters employing thermionic-valve circuits.

¹ [see BMB 613]

The results obtained with these devices are more accurate than those obtained with other methods. Serum electrodes have been devised which are capable of dealing with very small quantities of fluid—0.2–0.3 ml. In clinical bacteriology, the growth of cultures can be retarded, advanced, or even the manner of growth can be directed by proper pH control.

Thermostromuhr Apparatus

Reim (1928) introduced the thermostromuhr method for measuring blood-flow through a blood-vessel. A small insulator clip is placed around the blood-vessel. Two small plates which pass a radio-frequency current through the blood-stream are fixed in the central portion of the clip on opposite sides of the vessel. At each end of the clip there is a thermocouple differentially connected. These make contact with the vessel wall. The passage of the radio-frequency current through the blood-stream warms it slightly. The temperature-difference, which varies inversely with the blood-flow rate, is read electrically with a sensitive galvanometer. Calibration of the instrument is done by measuring the radio-frequency current used and adjusting a comparison-resistance to take the same current, thus permitting the dissipated wattage to be estimated. The constants of the blood-vessel clips are readily fixed by the application of a simple formula. A graph is obtained which permits this non-destructive instrument to be used almost as easily as a direct-reading mechanical flow-meter. This method has been improved upon by Essex, Herrick, Baldes & Mann (1936) and applied even to the coronary circulation.

Photo-cells

Light-sensitive devices have been responsible for some of the more recent developments of control engineering, as well as of sound reproduction and optical determination. There are three main types of photo-cell, the photo-conductive, the photo-electric and the photo-voltaic.

Photo-electric colorimeters are being used in many laboratories. They can be applied to practically every colorimetric problem, from the simple evaluation of intrinsic colour at portions of the visible spectrum to the more complex requirements of the analytical chemist.

A fall in haemoglobin-level is one readily detected sign of incipient malnutrition. Another use for a rapid haemoglobinometer would be in assessing minor degrees of anaemia among blood-donors. The photo-electric haemoglobinometer is more accurate than the visual method. In these, as green light is absorbed by a red solution (of oxyhaemoglobin), a constant source of light is used together with an appropriate green filter to pass a green light through the oxyhaemoglobin solution, the amount of light able to pass is measured by a photo-electric cell. The amount of light absorbed is proportional to the concentration of oxyhaemoglobin, and thus it is possible to construct a scale from which the percentage of haemoglobin can be rapidly and accurately determined. Bell & Guthmann (1943), among others, have devised a simple photo-electric haemoglobinometer.

Photo-electric colorimeters can be used for turbidimetric determinations just as readily as for colorimetric procedures. The basis for the calibration of these methods, which depend on the development of a uniform turbidity rather than a colour, is a solution of standard turbidity. Readings and results are obtained just as with coloured solutions. There are many applications of photo-electric turbidimetric methods, but only their use in penicillin assay will be mentioned here. Joslyn (1944) and McMahan (1944) among others, used such methods. Rantz & Kirby (1944) studied the action of penicillin on staphylococci by such a device.

Nygaard (1941) studied the kinetics and phases of blood-coagulation by means of a photo-electric device. His method depends on recording the amount of light transmitted through clotting blood to a photo-electric cell. A continuous photographic record of the diminution of the transmitted light can be taken.

Photo-electric Plethysmography

The basic principle of Leibel's method (1940) of measuring peripheral blood-flow is that the light intensity passing through a finger or toe on which a beam of light is directed will vary with the blood-volume within the part, and will thus be an index of the circulation through it. The emergent beam falls on a photo-electric cell which changes any variation

in the intensity of the light into a corresponding variation in an electric circuit. These electrical changes are amplified and then recorded with an electrocardiograph. Two practical applications of this method are the measurement of the pulse-velocity by superimposing the electrocardiogram on the tissue-circulation record, and the other is the demonstration in senile gangrene of increased blood-flow in the affected toe for some hours after the application of a Parvex glass boot.

Hertzman & Dillon (1940) have applied photo-electric plethysmography to the vascular reactions, such as Raynaud's disease, or in evaluating the completeness of sympathetic denervation of the skin, etc.

Radio-frequency Oscillators

The main uses of these devices in medicine are diathermy and short-wave therapy. These are so well known that it is not necessary to deal with them here.

Radio-frequency probe—Farmer & Osborn (1941) describe an apparatus for indicating the approximate position of metallic substances. Theoretically, the instrument should be of value in conjunction with x-ray examination. The principle is as follows. A radio-frequency oscillator works on a frequency of the order of 10^6 or 10^7 cycles per second and the whole of the turning-inductance of this oscillator is in the form of a search-coil capable of being moved about near the patient. If the search-coil approaches a metallic substance—such as a splinter in the operation area—the inductance of the coil will change, and hence, the frequency of the oscillator. The change of frequency can be made audible by heterodyning these oscillations with those of a second oscillator working on a slightly different frequency. A beat note can be detected which can be heard through a loudspeaker or headphones.

The Electron Microscope

The resolving power of a microscope is limited by the wave-length of light used. Moving electrons act as if they were associated with a wave-length. By using electron waves, 10^{-6} of the wave-length of visible light, much greater resolution can be got than with the optical microscope.

The electron microscope is classified as follows: the magnetic electron microscope, the electrostatic electron microscope, the scanning microscope, and the shadow electron microscope.

The electron microscope is of value in the study of viruses, bacteriophages, the combination of antibodies with flagellar and somatic antigens, the structure of bacteria, organic chemistry, etc.

The Cyclotron and Beta-tron

Rutherford, twenty-six years ago, performed the first mutation of one element into another, viz. nitrogen into oxygen, and directed attention to the means of energizing particles to such a degree as would enable them to penetrate the nuclear barrier of the atom. J. H. Lawrence experimented with lower voltages tuned to give the particles a series of pushes. Thus, the cyclotron was brought into being—an instrument in which the particle is kept moving in a circular path by a magnetic field, and intermittently accelerated by an electrical field. These particles move inside two hollow semicircular electrodes placed between the poles of an electromagnet, and are accelerated by an oscillating potential applied to the electrodes every time they cross the central gap between them. The angular velocity of the particle caused by the magnetic field is constant, but the successive acceleration of its linear velocity, caused by the electrical field, makes it move in an ever-widening flat spiral. The ultimate energy of the particle is limited only by the diameter of the hollow electrodes. Experimenters in nuclear physics, in the last ten years, had energies extending up to 16 million electron volts available in the form of high-speed positive ions from the cyclotron.

The three major fields of biological study developed about the cyclotron are: the use of a radio-active element to trace the absorption, utilization, and excretion of its stable isotope by the body in both health and disease; the therapeutic effect of the radiations emitted by radio-active substances internally administered; and beams of both fast and slow neutrons are being used in the treatment of cancer in a manner similar to x-rays and γ -rays in external therapy.

The cyclotron did not provide high-energy electrons as well as positive ions, because the light-weight electron behaves relativistically when its kinetic energy is still very small. Kerst (1942) gives details of the construction of an improved induction accelerator which gives electrons 20 million electron volts energy. The accelerator has a 19-inch [about 58 cm] diameter pole-face and weighs approximately 3½ tons [about 3,050 kg]. The x ray output, as measured in a thick-wall ionization-chamber, is 16 r.p.m. at one metre. The most important improvement incorporated in this accelerator is the electro-magnetic expansion of the equilibrium orbit, which can be tuned to send the electrons against the target at any desired energy up to 20 million electron-volts.

The high-energy x rays and electrons which are made available by the betatron can be employed for both physical experiments and practical purposes. It is probable that all the elements in the periodic table can be disrupted with the 20 million electron volts now available by a photonuclear

process. The energy of the x ray or γ ray is used, generally, in ejecting a neutron from the parent nucleus. The electrons of 20 million volts energy are capable of penetrating at least 10 cm into the human body. It has been suggested that they could be used therapeutically instead of x rays, and that they would have the advantage that the ionization produced by them would stop rather abruptly at about the middle of the body, and do no damage beyond. The betatron produces x rays which have intensities comparable with those produced by commercial machines. The maximum ionization caused by these x rays occurs at about 4 cm beneath the surface, which makes it possible to administer a large dose to the interior of the body without harming the surface.

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THE CLINICAL APPLICATION OF HEAT

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In view of the fundamentally important part which heat energy plays in the life of the human being, and the prominence of the physiological processes regulating the body temperature, it is remarkable that so very little is known about the quantitative administration of heat in clinical practice. In most cases the recommendation of heat treatment goes no further than the ancient prescription "Keep the patient warm." Coupled with our ignorance of quantitative administration there is also a remarkable lack of information about the exact therapeutic effects produced by heat. While it is generally true that by the application of heat energy the production of heat by the body can be supplemented to the advantage of the patient, we have to face the fact that, for instance, the application of a hot-water bottle produces an increase in body heat greater than the amount actually transmitted from the bottle. Clinicians are also aware of therapeutic effects produced by radiant heat at depths in the tissues quite out of the reach of the radiation employed.

Physical Basis of Heat Therapy

However, before all these questions can be discussed, we must first establish a basis for the dosage of heat treatment

and, since the methods of administration of heat are governed by the laws of physics, our first concern must be to establish a sound physical basis for clinical heat treatment. Normally the body disposes of about 100 kilogramme-calories of heat per hour, and it is therefore likely that therapeutic effects will be obtained only if the amount of heat administered to the body, or to part of it, approaches the total metabolic heat, or the proportion of this normally allocated to the part of the body in question. It is thus clear that, in contrast to x-ray or ultra-violet therapy which relies on a selective action of the radiation, in the case of heat application therapeutic effects will require the application of considerable energy. As in every other kind of therapy the chief danger to be guarded against is overdosage. From what has been said, two different kinds of overdosage can be foreseen. In the first place the tolerable concentration of heat input over a restricted area may be exceeded. When heat is applied to one square centimetre of the skin its temperature is raised and the degree to which this happens depends on the strength of the energy flow provided by the heat source, and on the capacity of the tissues to remove the local heating. With increasing heat-flow, removal processes are stimulated but

they will break down eventually and a serious local overheating of the tissues will be the result, in other words a burn will be produced. The limiting temperature above which the skin tissues must not be heated has been determined by Mendelssohn & Rossiter (1944), and has been found to be 45–50° C.

The other danger lies in the general application of heat. If the amount of heat applied becomes of the same order as the total metabolic heat, and especially if, in addition, normal methods of heat excretion (radiation and perspiration) are restricted, then the total heat balance of the body may be upset, and the patient may develop heat-stroke.

Methods of Heat Transfer

The physical distinction between methods of heat transfer is usually made as between convection, conduction and radiation. However, in the methods employed by the clinician, this clear distinction can rarely be drawn, for usually several modes of heat transfer are operative simultaneously. Pure convection is met with, for example, only in the case of a hot-air cabinet, and even here it may be necessary to consider also conduction through the air, and radiation from the heated walls of the cabinet. Methods relying mainly on conduction are met with more frequently, examples being hot baths, electric blankets and hot-water bottles. All these methods of conveying heat to the patient are admittedly convenient, but they present considerable difficulties from the point of view of quantitative control of administration. It is extremely difficult to discover how much heat the patient actually receives, for example, from a hot bath. The increase in body temperature produced can serve only as a very rough indication of the amount of heat received, for it must be remembered that as soon as heat is administered, the processes of heat removal are also speeded up. In addition, the ability to excrete heat may differ very considerably from patient to patient, and even in one and the same patient there may be changes according to the state of health.

A further difficulty in the application of electric blankets and heating pads arises from the time factor. As has been pointed out by Brown & Mendelssohn (1944) it takes more than an hour for an electric blanket to deliver heat at full strength.

Heat Transfer by Radiation

The administration of heat by radiation has proved to lend itself better than either convection or conduction to accurate measurement and quantitative dosage. It is for this reason that attention has been turned to this method of clinical heat application.

X rays, ultra violet rays, visible light and infra-red rays are all of a similar nature, and can all be classified under the heading of electromagnetic radiation. All represent a transport of energy, and when any of these rays is absorbed in a perfectly absorbing or "black" body, this energy appears as heat. The difference between these various types of radiation is solely that of difference in wave-length: the wave-length of x rays is from several thousand to several hundred times shorter than that of visible yellow light, ultra-violet rays are intermediate in wave-length between x rays and visible light. Deep-blue light with a wave-length of 0.45 μ represents the shortest wave-length visible to the eye, while red light with a wave-length of from 0.63 μ to 0.70 μ represents the longest visible wave-length. Infra-red radiation describes wave-lengths from 0.70 μ to 20 μ or more, and these merge imperceptibly into the short electric or radio waves. The wave-lengths used in radiant heat treatment are from the visible red up to, say, 20 μ .

In addition to the generalized heating produced when electromagnetic radiation is absorbed, specific effects may be produced, and these have been explained by the quantum theory. This theory states that radiation is not to be considered as a continuous flow of energy but as a shower of minute energy parcels or *quanta*, each representing an energy-contribution of a definite amount. Emission and absorption of radiation can only take place in whole or multiple quanta, never in fractions of a quantum. The energy-contribution of each quantum in radiation of a given wave-length is inversely proportional to the wave-length, i.e. the energy parcels of x rays are larger than those of ultra-violet rays, and these in turn are larger than those of visible light or infra-red radiation. The production of certain intra-molecular changes, for example, those leading to the production of

vitamin D in the tissues, requires the action of quanta of a certain minimum size peculiar to this particular change, that is, this change can be produced only by light of a wave-length sufficiently short to give quanta of the necessary size. The application of radiation of longer wave-length will not produce the same effect, even if large amounts of energy are supplied, simply because this longer wave radiation contains no quantum of the necessary size. The efficacy of x-ray and ultra-violet therapy depends on this fact. They are administered in small doses—only 10 gramme-calories or less at a treatment—and produce specific chemical changes in the tissues. They also, of course, produce heating of the tissues, but this is so slight as to be masked completely by the specific changes, even though the latter are caused by only a small proportion of the total incident energy.

The visible range of electromagnetic waves represents roughly the size of quanta below which no specific action is produced in the body tissues. In other words, the action of infra-red radiation is distinguished by the fact that it produces no specific reactions at all, and its absorption merely causes a rise of temperature in the tissues. The short wave radiations, such as x rays or ultra-violet rays, are limited in their application by the harmful effects which are produced by an excess of the specific changes for which they are responsible. Infra-red radiation, on the other hand, can be applied at a strength which is limited only by the capacity of the tissues to withstand heating. It is for this reason that infra-red radiation has become known under the name of "radiant heat" for, in contrast to the shorter wave length radiations, it offers a safe method of pumping heat-energy into the body.

To produce any sensible effect with infra-red, large doses, in some cases as much as 200,000 gramme-calories at a treatment, are used, but this infra-red radiation must not be accompanied by more than a minute proportion of ultra-violet radiation, which, in this case, would produce unwanted specific effects, and would severely limit the total energy which could be pumped into the patient without injury.

When a body is heated it emits electromagnetic radiation, and the total quantity of energy emitted from one square centimetre of its surface, as well as the wave-lengths in which this energy is emitted, depend on the temperature of the body. A body at 2000° K¹ emits 256 times as much energy from each square centimetre of its surface as a similar body at 500° K. For the first, the greatest intensity of radiation is in a wave-length of about 2 μ , for the second, the wave-length of maximum intensity is four times as great. Even a body at 4000° K, which is sixteen times as efficient an emitter of radiation as one of 2000° K, emits the greater part of its energy in the infra-red, but now there is an appreciable contamination with ultra-violet radiation.

In practice, the hot bodies used as sources of radiation are all at fairly low temperatures, and so provide radiation which is all in the infra-red with a little visible red light. An exceptional case is provided by the arc lamp, where the hottest part of the carbon rods may be at a temperature as high as 3500° C (3800° K) and gives a considerable proportion of ultra-violet radiation, even though the greatest part of the energy emitted is in the infra-red. Even an ordinary incandescent filament lamp actually emits a small proportion of ultra-violet radiation, but this is all absorbed in the glass of the lamp bulb.

At all temperatures, therefore, which may be acquired by the dull emitter heating-elements, or the metal shields and reflectors of radiant heat apparatus, the radiation emitted is in the infra-red, and, because of absorption by glass, the actual radiation which reaches the patient from an incandescent filament lamp is also infra-red, accompanied by a small proportion of energy in the visible region.

On the other hand, low-temperature sources are relatively inefficient, and hence, if we wish to secure a large total emission of radiation from the source, we must use extended sources, such as heated metal sheets, or groups of point sources. To illustrate this point the example of a heated metal sheet radiating to surroundings at room temperature may be quoted. At a temperature of 100° C this emits

¹ [It is convenient to give temperatures in degrees Kelvin or "absolute", which means the centigrade temperature plus 273°. The total energy radiated from a black surface is proportional to the fourth power of the absolute temperature, and other characteristics of the radiation are all most simply expressed in this temperature scale.]

only one calorie per minute from each square centimetre of surface

Calculation of Dosage

The x ray worker always has to deal with a point source of radiation, so that the radiation comes to his patient as a beam. For him it is a comparatively simple matter to calculate the dosage received by the patient from the strength of the source, the distance of the patient, the area irradiated, and similar data. In radiant-heat therapy with extended sources, such as, for example, radiant-heat cradles, there is no single beam of radiation, and each part of the patient's skin receives energy from all directions. It is possible to calculate the energy received on the skin from the strengths, temperatures and positions of the various parts of the source (Evans & Mendelssohn, 1944), but it is a somewhat severe mathematical problem, and is clearly an impossible method for ordinary clinical use. Reliance must be placed on direct measurement and what is needed is some simple method of measuring the energy actually received on the patient's skin.

In x-ray work, with beam therapy, a suitable standard of measurement would be the energy falling in one minute on a surface of one square centimetre placed normal to the beam. That was suggested by Mayneord & Tulley (1943) as suitable also for infra-red work, but, in fact, a slight amplification of their definition is necessary. A more suitable specification would be the total energy coming from all directions which impinges in one minute on a surface of one square centimetre placed in the position to be occupied by the skin of the patient. For a unit incident energy-flux of one gramme-calorie per minute we have suggested the name *pyron* (Evans & Mendelssohn, 1945).

This unit specifies the total incident energy without regard to wave length (colour, quality), but as the effect of all wave-lengths of infra-red radiation is simply to heat the tissues, the consideration of the range of wave lengths used in any given circumstances is of an importance secondary to the consideration of the total energy received in all wave-lengths. There are, of course, problems connected with the difference in penetrating power of different wave-lengths, but the first task is to provide convenient methods of determining the total flux.

Special Problems of Measurement

Before discussing practical methods of measurement we must first consider a theoretical point. As explained above, all hot bodies radiate energy, and cease to do so only if cooled to the absolute zero of temperature (zero on the absolute scale, see footnote, p 144). Hence all our surroundings continually radiate energy, and energy is being continually radiated from our skins to our surroundings. What we must measure, therefore, as being of clinical importance, is not the absolute amount of radiation-energy received from a clinical source, but the excess of radiant energy received on the skin, over that which would normally arrive from the surroundings. That is, we must compare the incident flux with that from surroundings at normal room temperature.

The fundamental physical method of measuring radiation flux is to absorb all the incident radiation on the blackened surface of known area of, say, a block of metal, and to determine the energy received from the rise in temperature of the receiver. Corrections must be applied for the cooling of the receiver which will lose heat by radiation and by conduction to the surrounding air. To eliminate the latter and to secure a rapid reading, the receiver is made of small heat-capacity, is placed inside an evacuated glass envelope, and its temperature is measured by thermo-electric methods. Estimates of intensity of infra-red radiation made with a vacuum thermopile are, however, liable to be very misleading in clinical practice, because the glass envelope absorbs all radiation beyond about 3.5μ , and we have found (Evans & Mendelssohn, 1944), that in certain clinically important cases, two-thirds of the incident flux may be beyond this limit.

The Thermo-radiometer

We have developed an instrument for the clinical measurement of radiation flux (thermo-radiometer) which dispenses with such an envelope. It consists of two receiver plates which are blackened and carry a pair of thermo-junctions on their reverse faces. The upper one receives the radiation

flux to be measured, while the lower one receives radiation from a surface maintained by water-cooling at room temperature, and which, therefore, emits the radiation characteristic of our normal

temperature surroundings. The two receiver plates are screened from one another by a small metal block, which has the effect of smoothing out random fluctuations of temperature. On the other hand, the two plates are very close together, and hence the air temperature for each of them is likely to be very nearly the same, so that the losses of heat

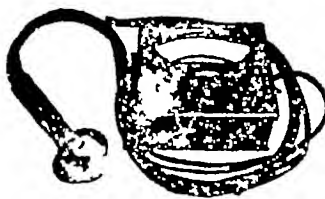


FIG 1. The complete thermo-radiometer, consisting of receiver unit (to be placed in the position of the skin area to be irradiated) and millivoltmeter calibrated in pyrons (gramme-calories per minute passing through a square centimetre). In addition to the current leads, tubes for water-cooling are attached.

by air conduction are practically the same for the two discs. Since the quantity which is actually measured in this arrangement is the fairly small temperature-difference between the two discs, all temperature-effects due to air conduction are cancelled. The lower, or reference, disc is screened from stray radiation which would falsify the readings, but a small air gap is left between the screen and the main part of the instrument through which a slow convection of air takes place. Without this air gap, layers of hot air might be trapped in the concavity of the water-jacket and would falsify the readings. We find that such an instrument registers a final reading in 30-40 seconds, and that it is accurate, certainly within 5%. It should be pointed out here that this accuracy is probably better than is needed in clinical work. What is needed is an instrument which, under varied conditions of use, will always indicate within a few per cent the total incident radiation. A vacuum thermocouple is more accurate in the sense that it measures a certain quantity

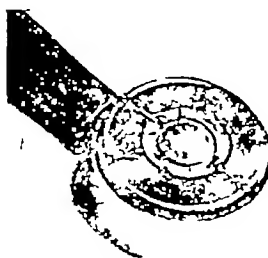


FIG 2. Close view of the receiver unit. The circular plate in the centre is the actual receiver plate which like a similar plate facing the water-cooled background, is suspended on the screening block.

very precisely, but as we shall see, under certain not unusual clinical conditions, the quantity which it does measure is very different from the quantity which the clinician needs for controlling his treatment. Our instrument must, of course, be calibrated against known radiation sources, or by other methods, but when this is done it is found to have a linear response, and the millivoltmeter or other instrument used to

measure the thermo-electric current may then be calibrated with a linear scale of pyrons. Typical examples of determinations of total flux under various clinical radiation sources are shown in the figures on p 146.

When this instrument is used to measure the incident flux under various types of clinical radiation source, it is usually found that the flux increases with time. This is due to the fact that the glass envelopes of the electric lamps, metal reflectors, and other parts of the source, become heated in course of time, and these in their turn become sources of radiant energy. The temperatures attained by these parts of the source are low, but in many cases they are of considerable area, so that they may eventually come to provide the major part of the flux received by the patient. On the other hand, the radiation which they do provide is all low-temperature long-wave radiation which is absorbed by glass. Hence, a glass-enclosed instrument will show little or no increase even under circumstances when, in the course of an hour, this instrument will show a three fold increase of flux. We have pointed this out in a discussion of radiant-heat cradles (Evans & Mendelssohn, 1944) where we found that the flux at the centre of the cradle increased from 0.4 pyrons to 1.2 pyrons in an hour. The patient, of course, will respond to this change in ways which may be unpleasant but for the reasons given, a glass-enclosed thermocouple will not respond to it. This time-factor is thus of peculiar importance in estimating radiant-heat dosage, its effects cannot be detected with a glass-enclosed instrument, but, if it is neglected serious overdosage and injury to the patient may ensue.

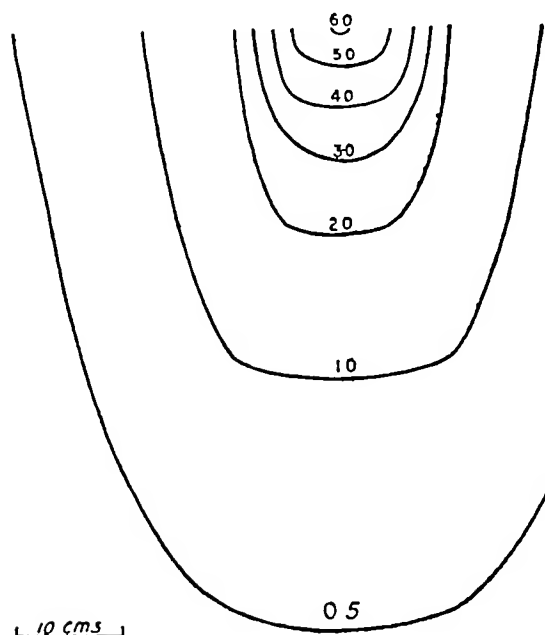
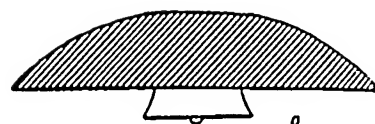
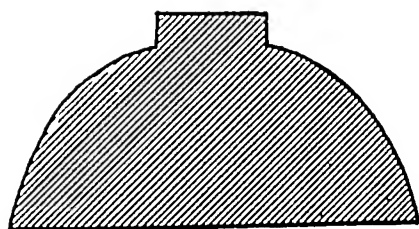


Fig 3a

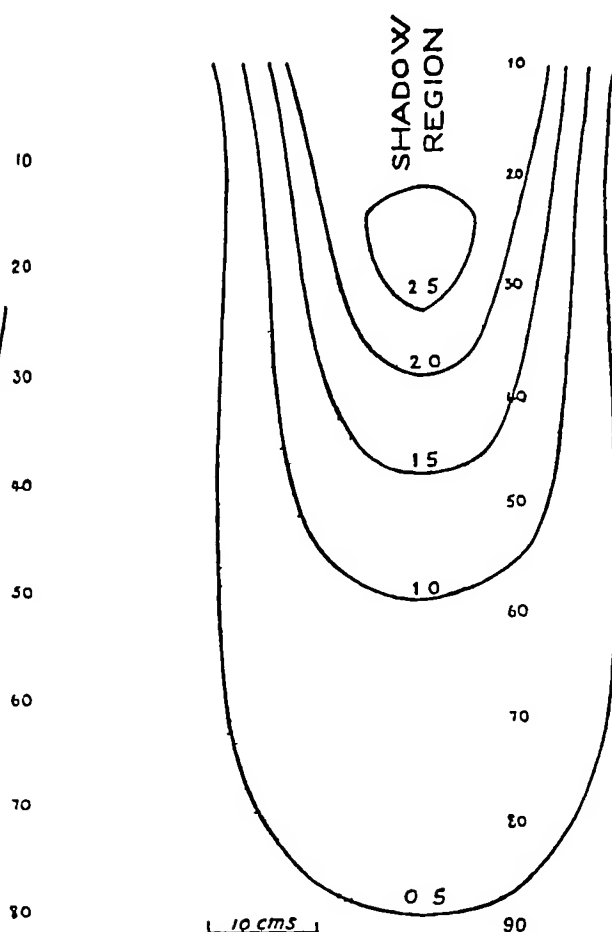


Fig 3b

FIG 3 Isophotes [curves of equal radiation-flux] from treatment lamps determined with the thermo-radiometer (receiver plate normal to the axis of the lamp) a, a bright emitter lamp of 1000 watts and b, a dull emitter lamp

Quality of Radiation· Transmission by Textiles

The study of the quality, or dominant wave-length, of infra-red radiation under conditions of clinical treatment is a difficult one, and little progress has been made. Some advance can be made by comparing different types of source,

such as, for example, an electric lamp (giving a radiation maximum at $\sim 1.5 \mu$) with an electric fire (giving a radiation maximum at $\sim 3 \mu$). Mayneord & Tulley (1943) have approached this problem by studying the absorption of radiation of different temperatures in various thicknesses of celluloid. However, as they point out, care must be taken in the interpretation of the results because of the scatter of radiation in this medium. This difficulty is, of course, aggravated in the case of infra-red radiation which is not administered in a beam. Secondary radiation from the filter may also cause falsification of results.

We have made preliminary experiments on the transmission by various types of textile materials (blankets, towels, cotton and linen sheets, lint, etc.) and find that, in general, materials transmit 20–30 % of the long-wave incident radiation, and 30–40 % of the short-wave. However, if a patient is covered by a blanket, it must not be assumed that he will only receive, say 25 %, of the energy incident on the upper surface of the blanket. In addition, the blanket will gradually warm up to a temperature depending on the particular circumstances, and will transmit energy, not only by secondary radiation, but also by conduction, both by direct contact and across air-pockets trapped between the blanket and the skin.

What is of importance is the total heat supplied to the patient by all mechanisms, and we have been able to evaluate the different contributions in one case. Before an open electric fire we found that a layer of lint transmitted 27.5 % of the incident radiation, and that conduction was responsible for transmitting an amount of heat equal to 32 % of the incident radiation. In this case the covering was not enclosed, and so the lint did not acquire a high temperature, and did not in consequence provide any appreciable amount of re-radiation. The total energy received on a calorimeter placed behind the lint was, in this case, 60 % of the incident radiation.

Conclusion

Thus, although some progress has been made during the past few years in the assessment of the physical factors

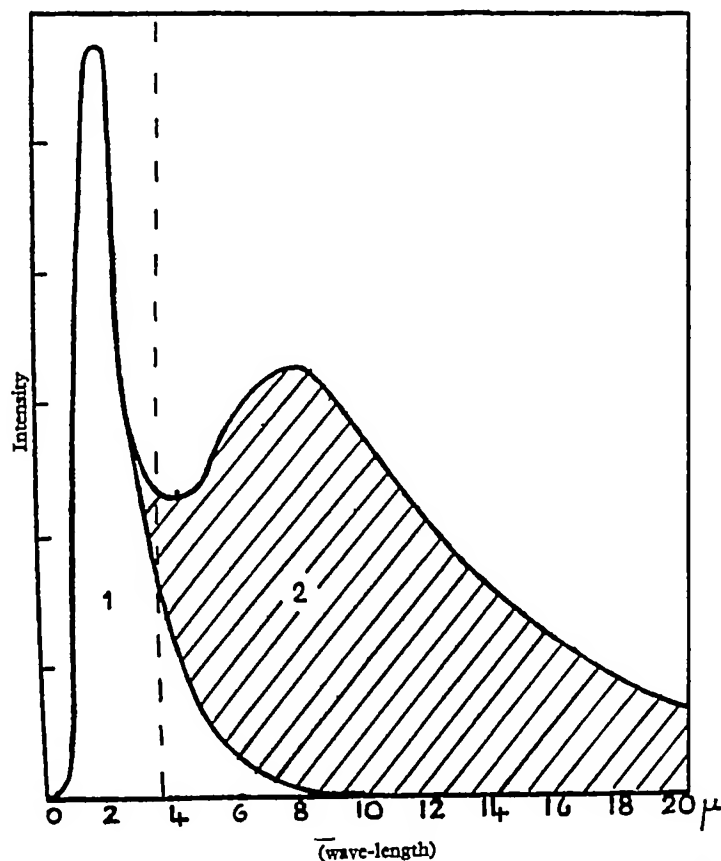


FIG 4. Wave-length distribution of radiant energy from a heat cradle. The area (1) represents the energy from the bulbs, which is all the energy emitted in the first minutes of treatment. The area (2) is radiation from the cradle background after one hour of use; the total energy emitted after one hour from switching on the cradle is represented by the sum of (1) and (2). The figure shows not only that the energy transmitted to the patient increases greatly with time, but also that the additional radiation from the background will escape detection if a glass-enclosed thermocouple is used. The wave-length beyond which glass will cut off all radiation is marked by the dotted line.

governing the clinical application of radiant heat, and in its quantitative measurement, very much remains to be done. In particular the physical details and clinical significance of the absorption processes of various wave-lengths in the tissues needs careful study. However, the most important problem of the clinical application of heat in general is the determination of limits of tolerance, together with the study of the relative therapeutic value of heat dosages of different magnitude. It is likely that, in this field of quantitative dosage, radiant heat will be found to be the method of admin-

istration for which quantitative control can most easily be achieved.

The work described in this paper on the physical factors governing the clinical application of heat constitutes a part of a general investigation of methods of administration and of the effects of heat treatment carried out in the Nuffield department of clinical medicine, Oxford University, and it is a pleasant duty to thank the director of this department, Professor L. J. Wits, for his interest and help at all stages of the work.

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THE MECHANICS OF BRAIN INJURIES

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There is some truth in almost all the theories of the mechanisms of brain injuries due to violence (Jakob, 1912, Sjoval, 1943, Anzelius, 1943), but in the writer's view (Holbourn, 1943, 1944a) only skull-bending, fracture, and rotation (Goggio, 1941) of the head are important. The physicist would attribute the comparative failure of most of the theorists to their wrong method of approaching the problem, in that they began by fastening their attention on a particular mechanism (e.g. coup and contrecoup, or production of cerebral anaemia). The physicist's initial assumption is that damage to the brain is a consequence, direct or indirect, of the movements, forces and deformations at each point in the brain. The movements, forces and deformations are not independent, so that it is sufficient to express everything in terms of deformations. These are worked out with strict adherence to Newton's laws of motion, but with approximations to the constitution and shape of skull and brain. Hence further advances can come only from making better approximations.

The Forces to be Considered

As a consequence of the principle of superposition, it is reasonably correct to assume in this particular problem that each cause produces its own independent injury. These causes may be regarded as (a) forces on the brain resulting from bending of the skull, (b) forces resulting from fracture of the skull or separation of sutures, (c) forces resulting from movement of the head as a whole and which would exist even if the skull were undeformable. (c) may be sub-divided into (c_1) linear acceleration forces, (c_2) rotational acceleration forces, (c_3) centrifugal forces, (c_4) Coriolis forces. Of these (c_3) and (c_4) are clearly negligible.

Now it is allowable to analyse the deformations of each infinitesimal element due to (a, b, c_1 , c_2) into two and only two types (α) change of shape, or distortion, without change of volume (this is analysed by physicists into a set of shear-strains) and (β) a change in volume without distortion. (α) is extremely liable to injure animate (Holbourn, 1944b) or inanimate objects. (β) is of two kinds (β_1) decrease in volume due to increase of hydrostatic pressure and (β_2) increase in volume due to decrease in hydrostatic pressure. Common sense suggests that (β_1) is harmless provided it does not cause prolonged occlusion of blood vessels. Its harmlessness has been verified for peripheral nerves (Grundfest, 1936). (β_2) is also harmless unless the decrease in pressure is sufficient to cause cavitation, i.e. liberation of bubbles of vapour or dissolved gases.

Changes in Volume

Unfortunately the terms "increase in volume" and especially "decrease in volume" are imprecise. Decrease in volume of a particular region might be brought about by

a true hydrostatic pressure acting equally in solid tissues, blood and tissue fluids, and not allowing anything to pass out of the given region. Under such conditions the ratio of the volume-decrease of a cm^3 of brain to the pressure-increase is the true compressibility and is the same as that of water, $5 \times 10^{-11} \text{ dyne}^{-1} \text{ cm}^3$. Alternatively the pressure causing the decrease in volume might act only on the solid tissue and might allow blood, or blood and certain tissue fluids, to escape from the region considered. Under such conditions one would obtain a pseudo-compressibility, whose value would depend on many things. A value of $2 \times 10^{-6} \text{ dyne}^{-1} \text{ cm}^3$ was found by Flexner, Clark & Weed (1932). It can be shown, however, that in any ordinary sort of accident very little blood or other fluid is forced out of the brain, and most of it will return when the blow is over. Hence, exsanguination is not the cause of immediate loss of consciousness, and the brain during an accident may be assumed to be nearly as incompressible as water. The medical man may, perhaps, be more easily convinced of the unimportance of immediate exsanguination by the observation that it is clearly not responsible for such things as massive haemorrhages into the temporal lobes, and that in slow crushing injuries, where exsanguination is greatest, there is no concussion (Denny-Brown & Russell, 1941). Of course, long after the blow is over, anaemia may occur owing to various pathological processes, but this is outside the scope of the present article.

Comparative Effects of the Forces Linear and Rotational Acceleration

To recapitulate, therefore, the forces (a, b, c_1 , c_2) are important only in so far as they give rise to (α), distortion (= shear-strain) or (β_2) decrease in pressure sufficient to cause cavitation.

On these assumptions bending of the skull (a) produces, owing to distortion, superficial bruising of the brain near the spot hit, combined with injury (usually negligible) where tissue is squeezed out of a foramen or defect, (b) causes distortion-injury to brain and blood-vessels near the fracture, (c_1) can be neglected because, as the brain is nearly uniform macroscopically in density, it causes almost entirely increases (β_1) or decreases (β_2) in pressure at every point. (β_1) as explained, is harmless. (β_2) would be injurious only if the pressure fell by, say, $5 \times 10^4 \text{ dyne/cm}^2$. Now, in the average accident, the pressure-fall due to linear acceleration is accompanied by a shear-stress in the brain due to rotational acceleration of about equal order of magnitude when expressed in dyne/cm^2 . But $5 \times 10^4 \text{ dyne/cm}^2$ of shear-stress would cause utter destruction of brain. Hence, in almost every accident, the linear acceleration, (c_1), can be neglected in comparison with the rotational acceleration, (c_2). There is an essential difference between linear and rotational movement. When the skull is moved in a straight line, it is the

brain's *incompressibility*, which prevents it from being left behind. This being very high, none of it lags behind, so that it moves as a whole, and there is no appreciable distortion (Fig 1). On the other hand, when the skull is

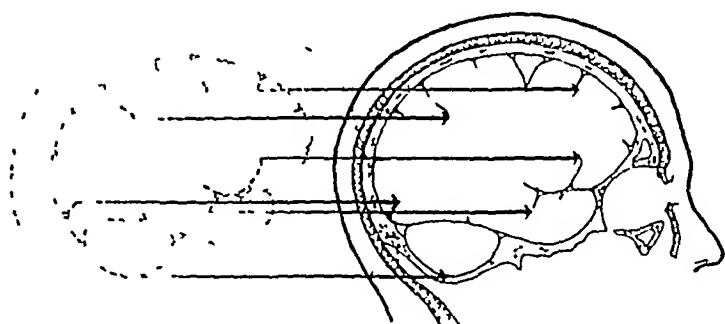


FIG 1 Absolute movement in space of the skull and brain when the skull experiences a linear acceleration. Arrows mark the actual paths in space of particles of skull and brain. The brain participates completely in the motion, each bit being pushed forward the requisite amount to keep step with the skull owing to the brain's extreme incompressibility. No part of the brain moves appreciably relative to the skull. Hence the brain suffers no distortion and therefore no injury.

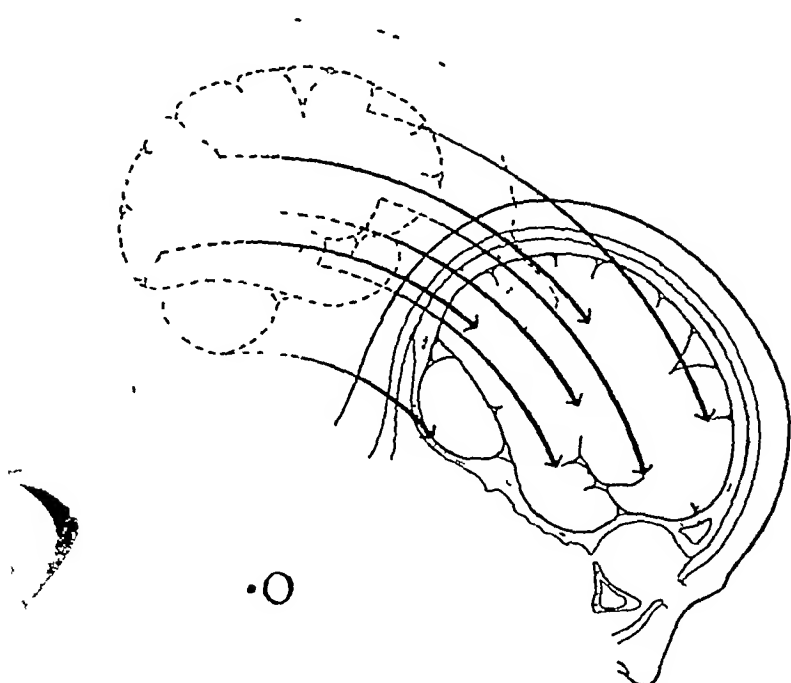


FIG 2 Absolute movement in space of a skull and hypothetical brain, supposed completely incompressible and completely rigid, when the skull is rotated about O. Arrows mark actual paths in space. The skull and brain move as a single rigid unit and the brain is not distorted.

rotated, the brain has to depend on its *rigidity* to avoid being left behind. But its rigidity is small, so that parts of it do get left behind to a considerable degree. It is therefore distorted (Figs 3a and 3b).

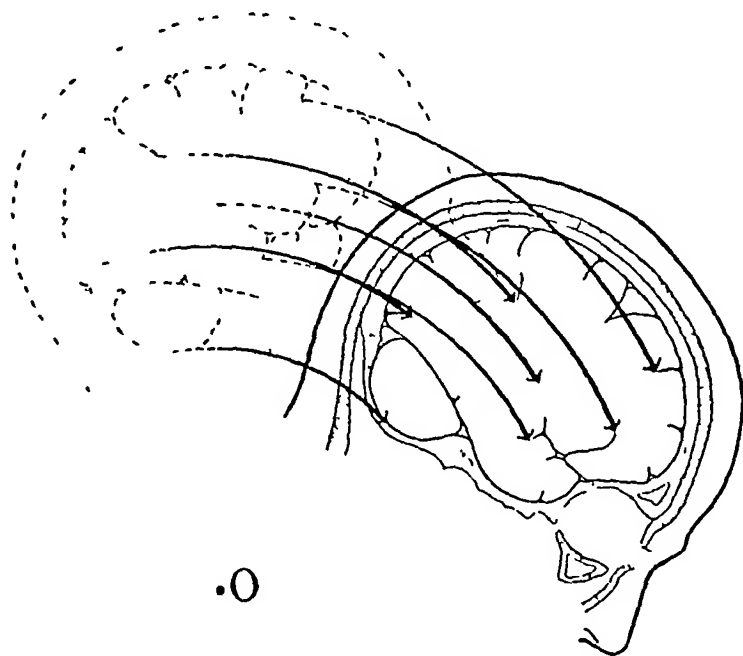


FIG 3a Absolute movement in space of a skull and real brain of small rigidity when the skull is rotated about O. Arrows as in Figs 1 and 2. Skull and brain do not rotate together as a single rigid unit. The brain moves relative to the skull and is therefore distorted and injured.

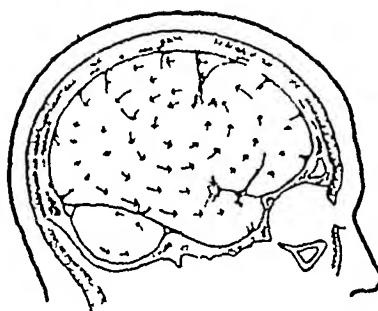


FIG 3b Relative movement of the brain with respect to the skull when the skull is rotated as in Fig 3a. In other words, this is a diagram of the lag of the brain behind the skull. The tail end of an arrow marks the starting position of a particle of brain relative to the skull and the point the final position, e.g. a sulcus moves in relation to the skull from the dotted position A to the full line position B. It is seen that the brain makes the only lagging movement open to an incompressible substance in an enclosed space, viz a whirling movement. The amount of the rotation and rotational acceleration, and is completely independent of the position of the point O in Fig 3a. Neither this figure nor Fig 3a are quantitatively accurate.

Distribution of Damage from Rotation

As rotation is theoretically so important, it is of interest to find the distribution of damage produced by it. This is done easily, though approximately, by making a model of a section of the brain out of gelatine and giving it a rotational jerk in a circular polariscope which renders the shear-strains in the gelatine visible. Fig 4 shows a system of shear-

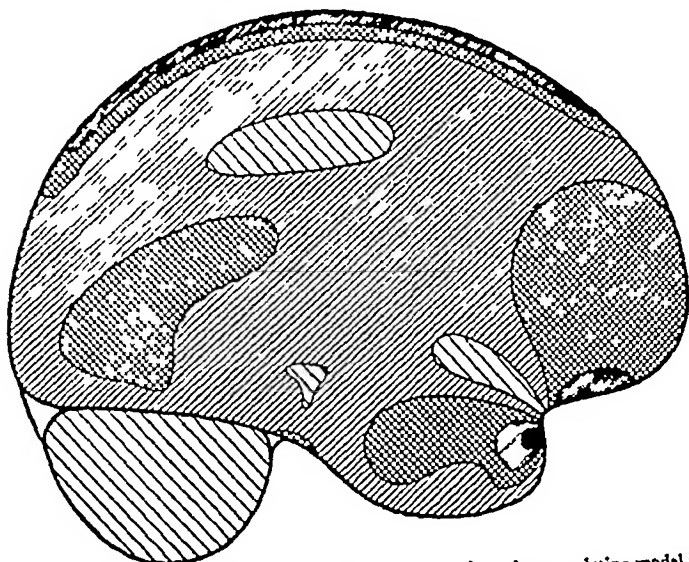


FIG 4 The shear-strains (= distortion) which arise when a gelatine model is rotated as in Fig 3a, or in the reverse direction. The darker the shading the greater the distortion. Note the comparative absence of distortion in the lateral cerebellar lobe and high distortion at tip of the temporal lobe.

strains obtained in this way. The good agreement with the findings at necropsy is to some extent fortuitous, as the following approximations have been made. There are no fissures or sulci in the model. The elasticity of the gelatine is uniform throughout the model, whereas white matter, for example, is stiffer than grey matter. This non-uniformity would tend to cause specially large strains near the junction between white and grey matter (Holbourn, 1944b). There is a two-dimensional strain-system in the model, but a three-dimensional strain-system in the brain. The brain has different rheological properties from gelatine, which nearly obeys Hook's law. On the other hand, differences in stiffness between gelatine and brain do not matter, in fact exactly the same strain-diagram would hold for glass or metal. Fig 4 refers only to blows of long duration.

Rotation causes the so-called contrecoup injuries, and presumably (as the effects of fracture and skull-bending are purely local) concussion. It follows that if the head can only rotate slowly, e.g. in the case of crushing between railway buffers, or is fixed, there is no concussion. The latter result agrees with that of Denny-Brown & Russell (1941), but not with that of Scott (1940). From a well-known theorem in kinematics it makes absolutely no difference to the rotational component of injury whether the rotation is one about an axis through the "centre" of the brain, or is an equal one about a parallel axis through the atlas or through Timbuktoo. But since the last case would involve a linear acceleration up to millions of miles per hour, the rotational component of injury would be comparatively unimportant. The rotational injury is approximately the same whether the head rotates forward from a blow on the occiput, or backward from a blow on the forehead. In both of these cases the damage is clearly symmetrical with respect to the mid-plane, but it is also approximately symmetrical with respect to the mid-plane whenever the head is hit at any point whatsoever by a blow whose direction is exactly perpendicular to the mid-plane. Such a blow causes a rotation about an axis lying in the mid-plane or parallel to it.

If the distribution in any region is sufficiently great, everything in that region that can be injured will be injured—blood vessels will be torn, axons torn, synapses disrupted, etc. The injury due to lesser amounts of distortion will depend on the degree of distortion, on the nature of the distorted region, and on the directions of the shear-strains relative to fibre-directions. But, in general, it must take less distortion to produce a quickly reversible effect in a cell body or axon than it takes to produce an actual tear in them or in a blood-vessel. The small distortions in a peripheral nerve produced by a falling drop of mercury or a jet of air are known to excite it without causing injury (Blair, 1935–36). It is reasonable to suppose that there is some similar sort of effect in the brain, and hence that blows so small that they produce no anatomical injury nevertheless momentarily upset the existing activity in the brain. Possibly momentary amnesia or the splash of light which often accompanies a blow are due to this effect. The shear-strains which arise as a result of squeezing a peripheral nerve can cause it to fail to conduct impulses, and if the strains have not been too severe the nerve will recover spontaneously after some minutes, even in the absence of a blood-supply. Once again, one would expect a similar effect in the brain. Amnesia lasting only a few minutes might be the result of such a mechanism.

Though the whole brain is distorted by rotation, some parts are much more distorted than others. Hence, so far as the physics of the problem is concerned, loss of conscious-

ness might be due to a diffuse neuronal injury, or to injury to a particular region, or both, or sometimes one, sometimes the other.

Conclusion

To sum up the position as it appears to a physicist in the vast majority of accidents to human beings, only skull-bending, fracture and rotation are of any importance, but, with sufficient experimental ingenuity, it would obviously be possible to produce injuries by other mechanisms. Some of the experimenters who report results due to the other mechanisms may have had this ingenuity, others may be misinterpreting their experiments.

The treatment given here needs modification in the case of injury by high velocity missiles.

POSTSCRIPT After this article had gone to press a film showing the surface of the brain as seen through a transparent window (Shelden, Pudenz, Restarski & Craig, 1944) was exhibited in England. It shows that in the case of a non-penetrating blow the surface of the brain slides several millimetres along the under-surface of the skull, no gap appearing between the two. Hence the brain is executing a swirling movement like that in Fig. 3b. Of course there is no proof that all the damage is due to the swirling, but no reasonable person who has seen the film can doubt its importance.

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¹ [BMB 622]

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HISTORICAL AND BIBLIOGRAPHICAL NOTES

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Some Points in the History of Clinical Thermometry

Although thermometry has become so much a part of the routine of clinical examination, it came into general use only within living memory, and after the clinical differentiation of most of the common fevers. Santorio (1561–1636) was the author of the first published description of the thermometer (or thermoscope) and of its use for the estimation of body temperature, but modern writers usually credit Wunderlich (1815–1877) with the establishment of thermometry in medicine, although he himself gave generous recognition to the work of his many predecessors. It is surprising in retrospect that some of the detailed observations on clinical thermometry published before Wunderlich did not excite more attention. It is true that Wunderlich's exhaustive treatise (*Das Verhalten der Eigenwärme in Krankheiten*, 1868) was far more systematic and conclusive than any that preceded it, but, in the words of one of his contemporaries,¹ "there is no better example of the truth that the success of a discovery depends upon the time of its appearance than that of the value of thermometry in disease".

Santorio did not describe the thermometer in his best-known work—*de statica medicina* (1614). Daresberg² and some later writers, including Garrison,³ gave his commentary on Avicenna (1625) as the source of the description, but Weir Mitchell⁴ and Sudhoff⁵ both give the earlier (1612) commentary on Galen. This is confirmed by Sherwood Taylor,⁶ who quotes a statement by Santorio in the earlier work that he had measured the temperature of "all places and parts of the body". The next reference to clinical thermometry is to be found in Boerhaave's Aphorisms (1709), in the 673rd of which he remarks that "external febrile heat is recognized by the thermoscope". His pupil van Swieten, in his commentaries (1745) on Boerhaave's Aphorisms, asserted that "by far the most accurate measurements of heat are by thermoscopes which are now to be had both elegant and portable". De Haen, van Swieten's colleague, reported important observations on clinical thermometry in various of the 15 volumes of his *Ratio medendi* (1759), and Wunderlich¹² says of him that his "very valuable data" have for the most part "been confirmed or even re-discovered in modern times". Virchow¹¹ described De Haen as the physician "who introduced the thermometer into the observation of the sick". Before the publication of Wunderlich's treatise Albutt, who independently took up

clinical thermometry in 1860, had been struck by the significance of de Haen's observations on the temperature in health and disease. Yet Garrison dismisses de Haen as having "coquetted with" clinical thermometry!

Before de Haen, George Martine (1702–1741), a Scot, published in 1740 what Wunderlich describes [erroneously referring to "Ch. Martin 'J' as "the first accurate observations on temperature in healthy men and animals". Garrison dogmatically refers to Martine's work as the only scientific treatment of the subject before Wunderlich", although a considerable number of writers of different nationalities published reliable observations on clinical thermometry during the latter half of the eighteenth and the early nineteenth centuries. Among these was James Currie (1756–1805), whose *Medical reports, on the effects of water* (1797) has been described as "the first series of English medical observations in which clinical thermometrical observations are systematically recorded"⁷ and as "singularly free from mere theories, and in the highest sense of the term, practical"¹³.

A fact not mentioned by any of the writers on the subject consulted is that Sir (then Mr.) Humphry Davy (1778–1829) apparently used clinical thermometry as a routine during the time that he was employed by Dr Thomas Beddoes at the famous Pneumatic Institution at Bristol. Davy's biographer, J. A. Paris, tells⁸ the following anecdote, which was communicated to him by the poet Samuel Taylor Coleridge (1772–1834). Shortly after Davy had (in 1799) discovered nitrous oxide, Beddoes ordered Davy to treat a paralytic patient by inhalation of the new gas. Before starting the administration, Davy inserted a small pocket thermometer under the tongue of the patient, as he was accustomed to do on such occasions, to ascertain the degree of animal temperature, with a view to future comparison.⁹ The paralytic man, misunderstanding the purpose of this novel procedure, declared that he already experienced the effects of its benign influence throughout his whole body.¹⁰ Davy cast a significant glance at Coleridge and resolved not to proceed with the administration of the gas. The patient attended for a fortnight's course of daily thermometry, and was discharged cured. The thermometric studies of Sir Humphry's younger brother, Dr John Davy, are mentioned by several writers.

The year 1850 marked a turning point in the development of clinical thermometry. F. W. F. von Bärensprung carried out investigations on the temperature in health and disease which were published in 1851 and which, according to Wunderlich transformed

a hitherto imperfect technique into a "comprehensive, well constructed, and, in many respects, complete doctrine." Independently, and probably¹³ after Bärensprung, L. Traube made observations on the temperature in disease which were published in 1850. In October 1851, Wunderlich himself, acting on the spoken recommendation of Traube, took up the study of clinical thermometry, and published observations in 1857, 1858 and 1860. By 1868, when his comprehensive treatise (*vide supra*) appeared, Wunderlich had made some millions of single observations on nearly 25,000 cases. In some respects his treatise makes strange reading to-day. The English edition¹³ contains 462 pages of text, of which no less than 22 are devoted to "The Art of Medical Thermometry"—which was by modern standards extraordinarily refined and elaborate. It is clear from this work that the diagnostic possibilities of thermometry were grossly overestimated. Faber⁴ has pointed out that the discovery of the characteristic temperature-curves of different fevers caused Wunderlich to modify his opposition to the views of those "ontologists" who affirmed the specificity of diseases.

Wunderlich advocated the axilla as the best site, and was opposed to the use both of the mouth and the rectum. That patients sometimes had their own views on this question is illustrated by Allbutt's assertion that rectal thermometry in those of the "coarser" class had "excited comments, the narration of which would not tend to edification."

Allbutt is commonly credited with having introduced the clinical thermometer in its present form, but the precise nature of his innovation is not clear from the statements to this effect. Sir Humphry Davy is described above as using a "small pocket thermometer", which he must have done between his discovery of nitrous oxide in 1799 and his departure from Bristol in 1801. According to Sims Woodhead & Varrier-Jones,¹² a description of a 5-inch portable thermometer was published in 1800 in the *Medical and Physical Journal*. Statements such as that made by Thompson¹⁰ that "Clifford Allbutt was the first to originate the present short instrument in 1867" would therefore seem to need modification. Woodman, Wunderlich's English translator, says that Messrs Casella [of London] were "the first to make a registering maximum thermometer for medical use" at the suggestion of "Dr Aitken" (*sic*). Allbutt also says that "the first clinical thermometers made in this country were those of Casella, under the direction of Dr Aitken"—apparently the Dr (later Sir) W. Aitken who followed and advocated Wunderlich's work on clinical thermometry as early as 1864. From Allbutt's statement above, the term "clinical thermometer" appears to be used as synonymous with "self-registering clinical thermometer." Allbutt describes how, finding Aitken's 10-inch thermometer inconvenient in private practice, he commissioned the firm of Harvey & Reynolds [of Leeds] to make a self-registering thermometer of 6-inch length, and later one of only 3 inches. It seems clear, therefore, that before Allbutt there were (a) short pocket non-registering clinical thermometers, (b) long self-registering clinical thermometers. Allbutt suggested a short self-registering clinical thermometer, which does not seem to be a very remarkable innovation.

N H J

- ¹ Allbutt, T. C. (1870) *Brit For med-chir Rev* 45, 429
- ² Daremberg, C. (1870) *Histoire des sciences médicales*, Paris
- ³ *Dictionary of national biography*, vol. 13, p. 341, London, 1888
- ⁴ Faber, K. (1923) *Nosography in modern internal medicine*, New York
- ⁵ Garrison, F. H. (1929) *An introduction to the history of medicine*, 4th ed., Philadelphia
- ⁶ Mitchell, S. W. (1892) *The early history of instrumental precision in medicine*, New Haven
- ⁷ Paris, J. A. (1831) *The life of Sir Humphry Davy*, London
- ⁸ Sudhoff, K. (1921) in Meyer-Stein, T. & Sudhoff, K. *Geschichte der Medizin im Überblick mit Abbildungen*, Jena
- ⁹ Taylor, F. S. (1942) *Ann Sci* 5, 129
- ¹⁰ Thompson, C. J. S. (1927) *Med Life*, 34, 510
- ¹¹ Virchow, R. (1895) *Hundert Jahre allgemeiner Pathologie*, quoted in Sudhoff, K. (1922) *Kurzes Handbuch der Geschichte der Medizin*, Berlin
- ¹² Woodhead, G. S. & Varrier-Jones, P. L. (1916) *Lancet*, 1, 173
- ¹³ Wunderlich, C. A. (1871) *On the temperature in diseases: a manual of medical thermometry* [English translation by W. Bathurst Woodman of the 2nd edition, 1870, of *Das Verhalten der Eigenwärme in Krankheiten*] New Sydenham Society, London

726/2

Thomas Young

"I must not pass by Dr Thomas Young, called Phenomenon Young at Cambridge, a man of universal erudition, and almost universal accomplishments. Had he limited himself to any one department of knowledge, he must have been first in that department. But as a mathematician, a scholar, a hieroglyphist, he was eminent, and he knew so much that it is difficult to say what he did not know. He was a most amiable and good-tempered man, too fond, perhaps, of the society of persons of rank for a true philosopher." Such was the opinion of Sir Humphry Davy¹ concerning Thomas Young (1773–1829), one of the greatest and most versatile of British scientists. At an early age he had mastered the rudiments of Greek and Latin, had read Newton's philosophy and knew a little Hebrew. While still at school he ground lenses and constructed his own microscope, learned to use the quadrant, and engaged in such activities as book-binding, colour-mixing and copperplate-making. On leaving school he studied the grammar of Hebrew, Chaldee, Syriac, Samaritan and Persian, and he made considerable progress in French, Italian and mathematics. He had

by the age of 17 mastered Newton's *Principia* and *Opticks*, besides translating considerable portions of Shakespeare into Greek.

In 1793 Young entered St Bartholomew's Hospital as a medical student. It was during his first year there that, while dissecting the eye of an ox, he perceived that the act of accommodation is due to a change of curvature of the crystalline lens, whereby light rays of various lengths can be brought to a focus on the retina. He published his findings in the *Philosophical Transactions of the Royal Society* (1793, 83, 169) and his paper gained for him the Fellowship of the Royal Society at the early age of 21. In 1801 Young, using the recently invented optometer, examined his own eyes, obtaining the focal length of the lens and other quantities such as the diameter, length of the corneal-retinal axis and the curvature of the cornea. This led to the important discovery that his eye did not possess equal power in focusing lines at different inclinations to the horizontal. Thus he made the discovery of astigmatism (*Phil Trans*, 1801, 91, 23). Young's explanation of colour-vision was corroborated in 1863 by Helmholtz (1821–1894).

Perhaps the best known of Young's contributions to science was his wave-theory of light. Before him Huygens had already claimed that light was a wave-disturbance, while Newton had maintained that it was a corpuscular phenomenon, i.e. that light was caused by the motion of minute bodies sent at high speed through space. Young's paper "On the theory of light and colours" (*Phil Trans*, 1802, 92, 12), read before the Royal Society in 1801, established the wave-theory and explained the phenomena of interference and dispersion. For some years Young's theory was opposed by several of his fellow-scientists, although in France Fresnel (1788–1827), working independently on the theory since 1814, was able to corroborate Young's findings.

In 1799 the Rosetta Stone was discovered in Egypt by the French. This stone was inscribed with a decree of Ptolemy Epiphanes in 3 characters—hieroglyphics, demotic and Greek. The stone was transferred to the British Museum and in 1814 Young commenced his study of it. Despite the fact that the early part of the hieroglyphic inscription was destroyed and that many parts of the Greek were mutilated, Young prepared a conjectural translation of the second (demotic) inscription. He was the first to grasp the idea of a phonetic principle in the reading of Egyptian hieroglyphics and to apply this principle in deciphering the inscription. He discovered and successfully applied the alphabetic hieroglyphics and elucidated other characteristics peculiar to them. Young's study of the writings of the Ancient Egyptians occupied part of his leisure from that time till his death, for in 1828 he finished his *Enchorial Egyptian dictionary*, which was published in 1830 as an appendix to Henry Tatton's *Egyptian grammar*.

During these years Young did not neglect medicine, for he had obtained his M.B. degree at Cambridge in 1803 and practised in London. He was appointed physician to St George's Hospital in 1811, a post which had some years before been held by William Hunter. An advocate of conservatism in treatment, Young made no great discoveries in medicine, although he attained some success as a sound teacher.

L T M

- ¹ Davy, J. (1836) *Memoirs of the life of Sir Humphry Davy*, London, 2, 365
- ² Oldham, F. (1933) *Thomas Young, philosopher and physician*, London
- ³ Peacock, G. (1855) *Life of Thomas Young*, London

726/3

Quincy on Physics in Medicine

In his introductory article to this number, Prof. Mayneord calls for a greater application of physical science to medical problems. A similar plea was made by John Quincy (*d* 1722) in his preface to *Lexicon physico-medicum*.

"I say Physics and Medicine, because the latter cannot subsist without the former. The Reader therefore on this View, will not wonder to find in a Work under this Title, a great deal about Attraction, the Laws of Motion, Gravitation, Air, Winds, Tides, Light, Heat, Cold, and the like, because he will find how they naturally lead to the Knowledge of some important Points of Practice, which, without such previous Lights, must lie hid in confusion, and upon the Hazard of Experiment and Guess-work.

And because what is brought from Physics and Mechanics takes up so much Room here, it may be necessary to inform the Reader, that there is no Knowledge in Medicine but by such Means. Experience without Theory will never make a Physician, any more than any other Practice can be obtained without an Acquaintance with the Rules on which it is founded, and he that is conducted only by Appearance, without being able to reason about their minutest Differences, will never see an Error till past Recovery.

If there be any thing of Science in Medicine, it is conducted by Demonstration, because conversant with Objects cognizable only by the Evidence of Sense, but without this, it is Chance and Confusion, and the Enthusiast and the Empiric are upon as good a Foot as the Scholar and the Physician. Not that I would be here understood to speak of Certainty in all Instances of Practice, because there are more Data required to that than the Nature of Things can admit of. But the Theorist will come at more of those Data than any other, and in every Step be able to compute all the Chances that are risked on either Side of a disputable Case, whereas the Empiric and the Experimenter are altogether in Uncertainty, having no Rules to make even Observation itself of real Use."

Quincy, whose writings exemplify the dominance of mechanical ideas on medical theory in the eighteenth century, was also the author of an English translation of Santorio's *Ars de statica medicina*.

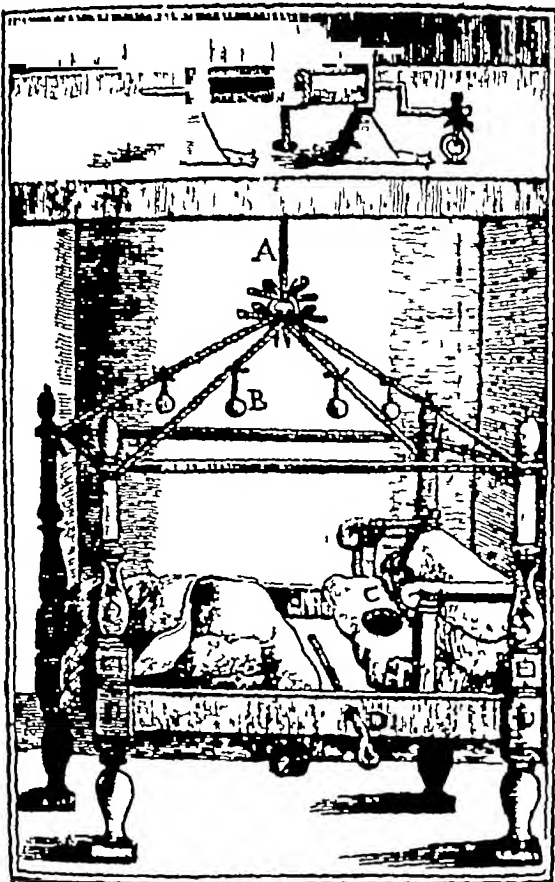
N H J

726/4

Santorio's Multiple-Purpose Bed: A By-product of Mechanical Medicine

The illustration below is taken from C. Daremberg's *Histoire des sciences médicales* (Paris, 1870), in which it was reproduced from the original (Venice, 1625) edition of Santorio's *Commentary on*

Avicenna, which also contains descriptions and figures of his thermometer, pulsilogium, and other instruments



Santorio (1561-1636) claimed six advantages for his bed (i) it could be used either as a bed or as an armchair, the rod D making it possible to lower or raise the mattress and bedclothes (E) (ii) the patient could relieve himself without leaving the bed, C is a mobile *chaise percée*, (iii) the bed could be suspended by means of the windlass and the cord A, or could rest immobilized, (iv) with the bed suspended, agreeable sleep could be procured by the "sweet music" made by collision of the hollow spheres (B), (v) a table could be laid on the chair-arms, (vi) the arms could be removed from the bed

N H J

726/5

A Physician-Physicist on the Study of Medicine

H L F von Helmholtz, to whom reference is made in Prof Mayneord's article in this number, looked back with pleasure and affection to his earlier experiences in the study and practice of medicine. In 1877, when Professor of Mathematical Physics at Berlin, he delivered a lecture on "Thought in Medicine", in which he said "Medicine was once the intellectual home in which I grew up, and even the emigrant best understands and is best understood by his native land."

In this lecture, Helmholtz paid the following tribute to his medical training.

"I consider the study of medicine to have been that training which preached more impressively and more convincingly than any other could have done, the everlasting principles of all scientific work, principles which are so simple and yet are ever forgotten again, so clear and yet always so hidden by a deceptive veil"

This lecture was published, with others, in an English edition in 1881

N H J

726/6

The Reception by the Medical Profession of the Discovery of X Rays

The centenary of the birth of W K Röntgen and the 50th anniversary of his discovery of x rays are both celebrated this year. It was in 1895 that he communicated his discovery to the Physico-Medical Society of Würzburg. A well-known physicist, Prof J A Crowther has recently given an interesting account of the discovery and its significance. Whether Röntgen chose to make this communication to a medical society because he foresaw the medical importance of x rays, or whether this happened to be the most convenient means of establishing his claim is not certain. "However this may be, the new radiation was taken up by members of the medical profession in all countries, in Britain among the first, with a zeal and devotion quite beyond praise. The pioneers among them began work with apparatus little more effective than, and quite as troublesome as, that with which Röntgen made the original discovery. Gradually, however, the insistent demands

of the medical radiologists for more and more penetrating power, and shorter and shorter exposures, bore fruit. With the realization that there would be a substantial market for x-ray equipment, engineers became interested in the problem. "—*Nature*, 1945, 155, 351-353

726/7

Surgeons of the name Bell

Benjamin Bell (1749-1806), a native of Dumfries, a leading Edinburgh surgeon of the eighteenth century and the author of a well known text book, was one of the first to confine his practice entirely to surgery. He tells us, in his autobiography, that his aunt married John Mowat, who was a surgeon at Longtown, near Carlisle. Mowat's father, also a surgeon, must have been a remarkable man. He died in 1776 at the age of 116 years. In his 100th year he performed the operation of lithotomy, and "some years later" he fractured his thigh by a fall in crossing the frozen River Esk, but soon recovered and continued his work as a country surgeon. Benjamin Bell was an ancestor of another Edinburgh surgeon, Joseph Bell (1837-1911), who was the original of "Sherlock Holmes".

Other eminent surgeons of the same surname, though not related to Benjamin, were John Bell and his more distinguished brother Sir Charles Bell (1774-1842). The former practised in Edinburgh, the latter spent most of his life in London, having acquired the Windmill Street School of Anatomy which the Hunters had made famous. There Sir Charles Bell conducted his researches on the nervous system which in his time won for him a fame almost equal to that of Harvey.

D G

726/8

Early Medicine at Aberdeen

Aberdeen was not only the first British university to include medicine in its curriculum, it was also the home of the author of the first original medical work to be printed in Scotland. In 1494, King's College, Aberdeen, was founded by Bishop Elphinstone "as a means of promoting the civilisation of the Highland clergy". The staff included a "Mediciner", who had a salary of £12 a year and the right of salmon fishing in the River Don. The third of the "mediciners", Gilbert Skene (or Skeyne), appointed in 1556, wrote a little treatise on plague, *Ane Breve Description of the Pest*, the first original medical work in the vernacular to be printed in Scotland. It appeared in 1568 and, so far as can be ascertained, the only copy known to exist is now in the National Library of Scotland. At the age of 53 Skene removed from Aberdeen to Edinburgh, where he conducted a large practice and became Physician to the King.

D G

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THE LIBRARY

Nature (1945, 156, 31) contains a long and interesting review of Professor Harry Friedenwald's *The Jews and medicine* (Baltimore & London, 1944), which is issued as a publication of the Institute of the History of Medicine at Johns Hopkins University. The reviewer, Dr Walter Pagel, describes the work as "the first comprehensive source book for the history of the Jewish physician".

De Pasteur a Fleming los antibióticos antimicrobianos y la penicilina (Editorial Plus Ultra, Madrid, 1945), by a distinguished Spanish microbiologist, Professor F Bustinza, provides for the Spanish-reading physician a broad survey of the development, nature, and uses of penicillin. The book, which is dedicated to Sir Alexander Fleming and Sir Howard Florey, is beautifully produced and profusely illustrated, and the earlier chapters on *Las bacterias*, *Los mohos*, and *La quimioterapia* provide the historical and general background which is essential to the intelligent understanding of the main subject. It is doubtful whether the medical or other reader in the Spanish-speaking world could find a better source of general information on penicillin than this book. It combines the merits of authority and exceptionally attractive presentation, and might well be made available in other languages.

Professor A V Melnikov, a surgeon consultant of the Soviet Army Medical Services has made an exhaustive study of the clinical features of sepsis in gunshot wounds. His monograph on the subject has now appeared in English under the title *Clinical aspects of sepsis in gunshot wounds*. It is translated from the Russian by Dr S Yale and is published by Medical Publications, Ltd at 15s [£0 75].

Penguin books are published at 9d. [£0 0375] each, and represent one of the most remarkable publishing ventures of modern times. In addition to the long range of literary classics, modern novels, and other works of general literature, this series now includes a considerable number of titles of medical and scientific interest, most of which are designated *Pelican* books, although issued by the same publishing firm. Many of these books have been published for the first time as *Penguins* or *Pelicans*, and some of them are of considerable originality—for example, *Cinebiology* (Darden, Field & Smith 1941), *Greek science its meaning for us* (Farrington, 1944), and *Mathematician's delight* (Sawyer, 1943). *A hundred years of photography* (Moholy, 1939) is an excellent short subject history which is obtainable only as a *Pelican* book. *Beyond the microscope* (Smith, 1943) is an admirable popular account of

viruses, in which most medical readers would find much unfamiliar and interesting material. Among the reprints of books previously available only in expensive editions are A. N. Whitehead's *Science and the modern world* and J. G. Crowther's *British scientists of the nineteenth century* (in two volumes).

However, it is a recent volume in the *Penguin* series, of special interest to medical readers, that has prompted this notice—*New biology 1* (edited by Johnson & Abercrombie, 1945). This contains 7 articles on biological subjects, some of which are by outstanding authorities: "The potato—master or servant" (R. N. Salaman), "The measurement of human survival" (L. Hogben), "Trace elements in plants" (W. Stiles), "The functions of the central nervous system" (J. Z. Young), "The anatomical basis of sensory experience" (W. E. Le Gros Clark), "Wireworms and war-time agriculture" (M. Miles), "Malaria, mosquitoes and

man" (M. L. Johnson). This volume is a good example of the notable contribution that *Penguins* are making to popular adult education.

The Association of Special Libraries and Information Bureaux (Aslib) has commenced publication of the *Journal of Documentation*, which is to be devoted to the recording, organization and dissemination of specialized knowledge. The first issue includes a paper on the "Origin and history of Aslib", by R. S. Hutton, and a "Draft plan for the publication of scientific papers", suggested by Dr N. W. Pirie, of the Rothamsted Experimental Station. The *Journal of Documentation*, which will appear quarterly, is issued free to members of Aslib. To others, the annual subscription is £1 5s [£1 25], and it may be obtained from Aslib, 52 Bloomsbury Street, London, W.C. 1.

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BOOKS, MEMORANDA, REPORTS

[The prices quoted are those which obtain within the United Kingdom. Editors of medical journals who wish to review publications of which notices appear below are invited to apply to the Editor for review copies, of which a few are sometimes available. Orders for any of the publications mentioned below may be sent to the Editor if there are difficulties in obtaining them locally.]

Publications may be referred to by the numbers given at the left of each item, preceded by the letters BMB, e.g. BMB 606/99. It should be noted that supplies of all publications are limited and there can be no certainty that publications ordered or requested for review will be available. Publications are classified according to the Universal Decimal Classification and the classification number is given at the right of each publication.]

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HUMAN EMBRYOLOGY

(Prenatal Development of Form and Function)

by W. J. Hamilton, J. D. Boyd & H. W. Mossman. Cambridge, W. Heffer & Sons, Ltd., 1945. 366 pages, 364 illustrations. 25 × 19 cm. £1 11s 6d [£1.575].

This is a straightforward account of human development which will doubtless be regarded as the standard textbook on the subject for many years. Although written primarily for students, it contains a great deal of information of value to teachers and advanced workers in this speciality. The early chapters deal with the formation of the germ cells, fertilization and cleavage of the ovum, and the implantation and growth of the embryo. Much of the work on these phases has been published relatively recently, and is now incorporated in a textbook for the first time. The finest illustrations of human material have been chosen from the international literature, and where necessary redrawn, and many of them are reproduced in colour. The changes in the maternal tissues and the physiological relationships between mother and embryo are considered in detail, and the experimental work on organization and differentiation is mentioned, but is not stressed.

Later chapters take up the development of the organ systems, and since there is less new material to introduce, follow more conventional lines. But together with an account of the appearance and development of each individual organ there is included an account of the region as a whole, such as is not usually found in student's textbooks. This anatomical outlook, well illustrated by sections, diagrams and models, helps to knit together as a natural whole the study of the life history of man. At the end of each section is a select series of references to the bibliography and a student should find no difficulty in grasping the fundamentals of his subject, and in following up any particular field in which he had become interested.

The main body of the work is devoted exclusively to human development, and work on other species is only introduced to illustrate phases not yet available in man, such as fertilization and implantation. In the last chapter, however, the early development of the vertebrates as a whole is surveyed briefly, and the more fundamental facts concerning the eggs, blastulation, gastrulation and the formation of the foetal membranes are considered.

The book is a production of the highest quality, the illustrations are well set out and beautifully reproduced, the bibliographies form a valuable appendix to each chapter and reflect the wide reading of the authors, and the index leaves nothing to be desired.

Chapter headings: (i) introductory concepts, (ii) formation, maturation and structure of the germ cells, (iii) cyclic changes in the female genital tract, (iv) fertilization, cleavage and formation of the germ layers, (v) the implantation of the blastocyst and the development of the foetal membranes, placenta and decidua, (vi) the fate of the germ layers and the formation of the essential (primary) tissues including the blood, (vii) growth of the embryo, development of external form, estimation of embryonic and foetal age, (viii) determination, differentiation, the organizer mechanism, abnormal development and twinning, (ix) cardio-vascular system, (x) alimentary and respiratory systems, pleural and peritoneal cavities, (xi) urogenital system, (xii) nervous system, (xiii) skeletal system, (xiv) muscle and fascia, (xv) integumentary system, (xvi) comparative vertebrate development.

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CATALOGUE OF LEWIS'S MEDICAL, SCIENTIFIC AND TECHNICAL LENDING LIBRARY

Revised to the end of 1943

published by H. K. Lewis & Co., Ltd., London, 1944. 928 pages. 21 × 13 cm. £1 5s [£1 25], 12s 6d to subscribers.

It is nearly 100 years since Lewis's Library was established to lend books on medical and scientific subjects not to be found in the ordinary circulating library. Since then, the library has been expanded to cover a wide range of technical subjects. The present catalogue includes about 24,000 titles, as the library carries many duplicates of the more frequently required books, it is estimated to contain 80,000 volumes.

The catalogue is a splendid piece of work, listing as it does almost every medical and scientific work published in English during the past century. It is divided into two parts, the first

contains author entries, while part 2 comprises a detailed subject index.

Perhaps the only important criticism of previous editions of this catalogue has been in connection with the omission of publishers' names. While it is appreciated that its primary purpose is to list books available in Lewis's Library, the catalogue has now become an indispensable reference work, both for librarians and readers, and its value as such transcends its original object of listing the books in the library. The publishers would do well to consider bringing it into conformity with other catalogues by including the usual bibliographical details. Nevertheless, they are to be congratulated both on the invaluable library which they have built up and on this excellent catalogue, which must have been produced under great difficulties. Our only criticism is the tendency, in the subject index, to classify according to title, with out reference to the actual volume, further subdivision of the subject index would be an improvement.

Perhaps the centenary of this important library in 1948 will be

celebrated by a new edition of the catalogue, incorporating the foregoing suggestions. Such a volume would be given a permanent place among special bibliographies, besides adding one more service to the many which have been rendered by "Lewis's"

727/140

A MANUAL OF ZOOLOGY

by L. A. Borradaile. 11th edition. London, Oxford University Press, 1945. 813 pages, 551 illustrations. 18 x 12 cm. £1 4s. [£1.2]

Two classes of reader are served by this manual—those taking a general course in zoology, and those studying the subject in preparation for a preliminary medical or similar examination. The book, which provides a comprehensive introduction to the subject, and is copiously illustrated, is one of the best known short texts on zoology. The writer was at one time lecturer in zoology in the University of Cambridge, and his wide experience in teaching the subject is manifest in the book. An exhaustive index is provided.

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GALEN ON MEDICAL EXPERIENCE

First Edition of the Arabic Version, with English Translation and Notes by R. Walzer

London, published for the trustees of the late Sir Henry Wellcome by the Oxford University Press, 1944. 164 pages. 25 x 18 cm. 12s. 6d. [£0.625]

The first appearance in print of the treatise *On medical experience* written by Galen at Pergamos during the 2nd century A.D., constitutes an important, and even an astonishing event in the history of medical literature. Still more surprising is the freshness and modernity of Galen's argument, indeed, his treatise, so many centuries old, might serve as an inaugural lecture, or as a graduation address to-day. The author deals with the age-long discussion of the relative advantages of Dogmatism and Empiricism, of theory and practice, of knowledge and experience. Such a problem has formed the subject of many a debate since Galen's day because, although a judicious mixture of the opinions of both sides was eventually sponsored by Galen himself and has been accepted by many leaders of medical thought in the centuries which followed, there has been constant evidence of a bias in one or other direction.

At the present time, medicine is overburdened with detail and technique to such an extent as wellnigh to exclude the background of general principles. The fact that systematic knowledge is an essential basis for fresh observation is almost forgotten. Galen leads us back to the foundations of medicine. In the present treatise he takes the side of Empiricism, emphasizing the value of experience and pouring a torrent of cynical remarks upon those Dogmatists who would have medicine reduced to a rule-of-thumb science. "Just at what point," he asks them, "does a hill become a mountain, and how many people are required to form a nation?" Such facts, he argues, cannot be stated in measures or numbers, although most men are agreed regarding them. Those things are to be learned from experience alone.

No brief extract from the treatise, however, can convey a clear idea of its contents. It must be read in its entirety, and it cannot be regarded as easy to read or simple to understand. Nevertheless it contains much that is of value to the modern medical man, and it may well serve to stimulate interest in the neglected subject of medical philosophy. Scholars will welcome it as an important literary landmark.

The manuscript of the work was discovered in 1931 at Istanbul by Dr H. Ritter. It was written in Arabic, a translation from the original Greek text of Galen having been made, first into Syriac by Hunan, the renowned translator of the School of Gondisapor in Persia, and then, from Syriac into Arabic, by his nephew Hubalsh. The Arabic text is printed in the present book, followed by an English translation by R. Walzer, who bears a high reputation as an Arabic scholar. The work has been beautifully produced at a remarkably low price.

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THE INFANT

A Handbook of Management

by Wilfred J. Pearson & Arthur G. Watkins. Third edition. London, H. K. Lewis & Co., Ltd., 1945. 60 pages. 18 x 12 cm. 4s. [£0.2]

The simpler and more practical rules for the care and feeding of infants are given in this short book. Some of the information is otherwise available only in the larger text-books and it should therefore make a special appeal to infant welfare workers, medical students, midwives, etc. In this new edition, sections on preventive inoculation and vitamin requirements, values and sources have been included.

Dr. Pearson is physician in charge of the children's department, University College Hospital, and physician, Hospital for Sick Children Great Ormond Street, London. Dr. Watkins is physician in children's diseases, Cardiff Royal Infirmary.

Chapter headings: (i) general rules for the feeding of infants—including breast feeding, (ii) artificial feeding, (iii) the care of the premature or immature infant—under 5½ lb, (iv) character of stools, (v) general rules for the care of the child, (vi) preventive inoculation, (vii) stages of growth and development, (viii) diet

tables, (ix) recipes, subcutaneous infections, blood transfusion, hypodermic injections, (x) food value tables, (xi) vitamin requirements, values and sources.

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THE ELEMENTS OF MEDICAL TREATMENT

by Sir Robert Hutchison. Fourth edition. Bristol, John Wright & Sons, Ltd., 1945. 213 pages. 18 x 12 cm. 10s. 6d. [£0.525]

For several years Sir Robert Hutchison gave an annual course of lectures on elementary therapeutics. These were later expanded into book form, to provide an excellent account of the principles of treatment and their practical application to the commoner diseases. The book has passed through several editions and has become well known to medical students.

Recent advances in treatment have made necessary, in this fourth edition, an extensive revision of the text and the insertion of a new chapter on chemotherapy. As in earlier editions, special attention is given to the prescription of drugs.

Chapter headings: (i) some general principles, (ii) fever, diaphoretics and antipyretics, (iii) pain, analgesics, (iv) insomnia, hypnotics, (v) constipation, purgatives, aperients, and enemata, (vi) diarrhoea, astringents, (vii) heart failure, heart stimulants, heart tonics, diuretics, (viii) bronchitis, expectorants and antispasmodics, (ix) anaemia, haematinics, (x) high blood-pressure, vasodilators, (xi) gout and gravel, uric-acid solvents and lithontriptics, (xii) drugs that act upon the urine, urinary antiseptics, (xiii) dyspepsia, stomach mixtures, (xiv) intestinal parasites, anthelmintics, (xv) disease of the gall-bladder, cholagogues and biliary antiseptics, (xvi) nephritis, (xvii) haemorrhage, haemostatics, (xviii) tonics and sedatives, (xix) diabetes, insulin, (xx) endocrine treatment, (xxi) chemotherapy, (xxii) specific treatment (bacteriotherapeutics), (xxiii) physiotherapy, (xxiv) psychotherapy, (xxv) some minor medical operations.

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ACTINOTHERAPY AND DIATHERMY

For the Student

by E. B. Clayton. Third edition. London, Baillière, Tindall & Cox, 1945. 204 pages, 55 illustrations. 20 x 13 cm. 8s. 6d. [£0.425]

Dr. Clayton is director of the physical treatment department of King's College Hospital. In writing this book he has attempted to provide an account of the subject sufficient to cover the requirements of students working for part 2 of the Chartered Society of Physiotherapy examination. Part I of that examination is provided for by the author's *Electrotherapy with the direct and low frequency currents*, 1944.¹

Part I contains six chapters dealing with all aspects of heliotherapy. Part II deals with diathermy and has the following chapters: (vii) physics, (viii) high-frequency current of low amperage, (ix-x) long-wave diathermy, (xi) short-wave diathermy, (xii) long- and short-wave diathermy. The chief changes in this new edition occur in Part II, and chapter viii appears for the first time.

¹ [BMB 682/124]

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A SYNOPSIS OF MEDICINE

by Sir Henry Letheby Tidy. 8th edition. Bristol, John Wright & Sons, Ltd., 1945. 1,215 pages. 18 x 13 cm. £1 10s. [£1.5]

It is 6 years since the appearance of the previous edition of this well known *Synopsis*, and the author reminds us that during that period the greatest advances in medicine have been in the region of treatment. The early promise given by the sulphonamides has been fulfilled, and the book records the most important uses to which drugs of this group can be put. The author has considered it wiser to omit reference to the use of penicillin, as the knowledge of its action is still advancing rapidly.

The chapter on haemolytic disease of the newborn now includes information on the Rh factor. Vitamin K is dealt with for the first time, and there is a new article on sex hormones. Four important diseases previously considered only briefly are now more fully described: primary atypical pneumonia, acute encephalomyelitis, congenital cystic disease of the lung, neoplasms of the bronchus. Articles which have been extensively rewritten include aetiology of influenza, treatment of malaria, yellow fever, typhus fevers, effects of heat, poisoning by coal-tar derivatives, staphylococcal food poisoning, vitamin B₁, vitamin C, silicosis, asbestosis, peptic ulcer of the oesophagus, diaphragmatic hernia, porphyria, myohaemoglobinuria, haemolytic anaemias of the newborn, chronic constrictive pericarditis, coronary occlusion, essential hypertension, hypertensive encephalopathy, sciatica, anxiety neurosis. Numerous other additions and alterations have increased the size of this edition by about 40 pages. There is no doubt that in this edition Tidy will retain its position as the leading synopsis of such knowledge of clinical medicine as is of importance at the present time.

The book contains 186 chapters arranged under the following sectional headings: (i) specific infectious diseases, (ii) diseases due to physical agents, (iii) the intoxications, (iv) diseases of metabolism, (v) diseases of deficiency, (vi) diseases of the digestive system, (vii) diseases of the respiratory system, (viii) diseases of the kidney and urinary tract, (ix) diseases of the blood and spleen, (x) diseases of the circulatory system, (xi) diseases of

the endocrine glands, (xii) diseases of the nervous system, (xiii) vasomotor and trophic disturbances, (xiv) diseases of the muscles, joints, and bones

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THE PAPWORTH FAMILIES

A 25 Years Survey

by E. M. Brieger With a preface by Sir Arthur Salusbury McNalty
London, William Heinemann (Medical Books) Ltd, 1944 674
pages; Illustrated 22 x 14 cm £2 5s [£2.25]

Papworth Village Settlement, founded in 1916 by the late Sir Pendrill Varrier-Jones, represents one of the most comprehensive schemes in existence for the care of tuberculous men and women. It provides prolonged medical and surgical treatment, associated when possible with clerical or industrial training designed to maintain or improve the patient's working capacity and earning ability. In addition, it provides the opportunity for as many patients as possible to earn, and, recognizing the importance of after-care, it enables the patient to whom the opportunity to earn has been given, to live in the village settlement with his family.

It has thus been possible for a very careful observation to be made of the health of the families residing in the Papworth community. A vast and unique record consisting of more than 5,000 x-ray films and a great collection of clinical records has accumulated. This material has been carefully studied by Dr E. M. Brieger, a member of the Papworth research staff, and the results of its analysis form the substance of this book. A survey of the whole literature concerning the history and infectivity of tuberculosis forms the starting-point from which the results achieved at Papworth are discussed. Two groups of children are the central point of the investigation, 151 children, accompanied by their mothers, came to live with their fathers at Papworth Village, and 108 children had been born in the village when the survey was completed. Their health has been the subject of unremitting care, and the clinical records made possible are a most valuable addition to the literature on the subject. Seldom in clinical investigations have individual cases been made the subject of such accurate and meticulous observation.

Of the 151 children admitted to Papworth, 4 had juvenile tuberculosis and 9 developed pulmonary tuberculosis of the adult type. Of the 108 children born in the village, none has, while a member of the community, developed tuberculosis in any known clinical form. Those who have left to seek education or employment elsewhere are all free from the disease.

The results discussed in this book are fully documented, and the publication of this survey, besides being a unique contribution to our knowledge of contact infection, stands as a splendid memorial to the founder of Papworth and a model of tuberculosis research. The book, which includes an extensive bibliography, was itself printed and produced at Papworth.

Chapter headings Part I Historical introduction (i) anticipations, (ii) conflicting evidence, (iii) interpretations. Part II The Papworth Village Settlement (iv) the method of investigation, (v) the Papworth community, (vi) the Papworth families, (vii) incidence of the various types of lesions in village-born children, (viii) incidence of the various types of lesions in admitted children, (ix) family epidemics in admissions, (x) intermarriages and child-birth, (xi) case types, (xii) conclusions. Part III Epidemiological interpretation (xiii) comparative statistics, (xiv) natural resistance, (xv) acquired protective immunity, (xvi) heredity. Part IV Pathological implications (xvii) clinical pattern of air-borne contact infection, (xviii) initial phase, (xix) the interval, (xx) the onset of pulmonary phthisis, (xxi) epilogue. Appendix case histories of the Papworth families, x-ray films 2 families, illustrating family epidemics, facsimile reproductions of survey tables, standard works with abstracts and bibliography.

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616-002 5-083

AIDS TO TUBERCULOSIS FOR NURSES

by L. E. Houghton and T. Holmes Sellors London, Baillière, Tindall & Cox, 1945 246 pages, 16 plates and 58 figures
16 x 11 cm 4s [£0.2]

In the larger tuberculosis sanatoria in Britain a two years' training scheme is in operation, for the benefit of nurses wishing to take the

certificate awarded by the Tuberculosis Association. Holders of this certificate are recognized as having reached a high standard of proficiency in this branch of nursing.

This small book, one of the *Nurses' Aids* series, is intended both as a text-book to cover the syllabus of the Tuberculosis Association Certificate and as a reference book for nurses working at sanatoria as part of their general training. It gives a straightforward account, by a physician and a surgeon who are both well known as authoritative writers on the subject, of the pathology of tuberculosis, together with a description of the main clinical features of the disease. When discussing therapy, the book emphasizes the institutional aspects of the treatment of pulmonary tuberculosis. A special section, contributed by E. T. W. Starkie, is devoted to the nursing of non-pulmonary tuberculosis.

Chapter headings (i) the nature of the problem, (ii) variations in the disease, (iii) the tubercle bacillus, (iv-v) morbid anatomy, (vi) aetiology, (vii) symptoms of pulmonary tuberculosis, (viii) treatment of pulmonary tuberculosis, (ix-x) sanatorium régime, (xi) the complications of pulmonary tuberculosis, (xii) conditions associated with phthisis, (xiii-xv) collapse therapy, (xvi) tuberculous empyema, (xvii) differential diagnosis, (xviii) tuberculosis of bones and joints, (xix) abdominal and uro-genital tuberculosis, (xx) prevention.

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616 15

CLINICAL ATLAS OF BLOOD DISEASES

by A. Piney & Stanley Wyard Sixth edition London J & A. Churchill, Ltd, 1945 138 pages, 48 plates 21 x 13 cm 16s. [£0 8]

The appearance of a sixth edition of this small book only fifteen years after the first indicates that it fulfils the needs of many medical men. The authors state that primarily the work is to be regarded as an atlas, and therefore the display of blood- and marrow film pictures is the feature to which most attention should be directed. It is well known that the path from the actual field of a blood-film seen down the microscope to its reproduction in a printed book is fraught with many hazards, with the result that such reproductions are often inexact. However, the diagrams in this book show how greatly the technique of colour printing is improving, and they raise the hope that true facsimiles will soon be possible for all cells.

In a publication of this type, the diagrams should be such that they are of definite assistance to the reader who is attempting to understand the key features of films from cases of his own. In the majority of instances this is certainly the case here, but on quite a few occasions the typical features are not well enough emphasized. For example, the highly characteristic nuclear pattern of megaloblasts is poorly shown in the pernicious anaemia marrow-films, and the erythrocytes depicted in the blood-film for idiopathic hypochromic anaemia do not contain the typical central pallid areas. With the increasing use of marrow punctures for diagnosis, more diagrams showing the changes in diseases where such punctures have real diagnostic value could have been profitably given. An outstanding example is multiple myelomatosis.

Opposite each diagram, and between successive ones, short summaries of the salient features of the corresponding and allied diseases are given. The very brevity of these descriptions makes them inevitably inaccurate and misleading on occasion. As the book is intended primarily for practitioners and physicians, much might have been gained if the clinical and general pathological features had been omitted, and the resultant space devoted to a fuller description of the haematological details and of their relation to the corresponding signs and symptoms. Further, the introduction into this book of descriptions of diseases in which blood pictures yield little information of diagnostic value is out of place, as for example in haemochromatosis. Finally, a print of uniform size is preferable to the varied ones used here. If different types are necessary, then those of larger size should be used for conditions of common occurrence, and the smaller ones for the rare diseases. The reverse is unfortunately often found here.

In spite of the few limitations indicated above, this book is useful as a standard of pictorial reference, and will prove especially helpful to the physician who makes the very proper attempt to understand the blood changes which occur in the patients under his care.

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FILMS

[This section appears for the first time. It will in future appear regularly or intermittently, according to the supply of suitable British films. Many of the older films will not be noted here, and others will be omitted because of technical imperfections, unrepresentative presentations of the subject, or merely because we have not seen them. Overseas medical teachers and medical societies who wish to borrow or purchase prints of the films indexed or reviewed here should apply to the nearest British Council representative (see inside back cover) or direct to the Editor, quoting the numbers used below, preceded by the letters BMB, e.g. BMB 728/2. Inclusion of a film in this section does not imply that a print will be available for loan or purchase. In some cases it will be, and in others it will not.]

728/1

I.C.I. ANAESTHESIA SERIES NO. 4 THE CARBON DIOXIDE ABSORPTION TECHNIQUE

made by Reallist Film Unit, 1945, owned by I.C.I., 16 mm sound, 880 ft [260 m], 35 mm sound, 2210 ft [660 m], 3 reels, black and white, 25 minutes

This film illustrates the use of the soda-lime absorber in anaesthesia. An introductory diagram shows the effects of re-breathing

with and without absorption of carbon dioxide, the use of the soda-lime canister is then demonstrated in detail, with many useful practical hints. After dealing with the simplest apparatus, the principle of the more complicated closed-circuit instrument with directional valves is illustrated admirably by an ingenious diagram. This apparatus is then shown in use with ether as the anaesthetic agent. Finally, there is a demonstration of the technique of controlled respiration by artificially induced apnoea, and the principles of this procedure are illustrated diagrammatically, although this

diagram is rather too complicated. Both this film and the following one [BMB 728/2] are first-class teaching material. There is a very high standard of photography and film technique throughout, and every point is made absolutely clear by careful demonstration of simple, practical apparatus.

A F-C.

728/2

I.C.L. ANAESTHESIA SERIES NO. 9 RESPIRATORY AND CARDIAC ARREST

made by Realist Film Unit, 1945, owned by I.C.L., 16 mm. sound, 530 ft. [160 m.], 35 mm. sound, 1330 ft. [400 m.], 2 reels, black and white, 15 minutes.

This film describes the two most important and most alarming emergencies with which the anaesthetist may be faced. The symptoms and causes of respiratory arrest under anaesthesia are first illustrated and, after this, various methods of resuscitation, such as the provision of a free airway, the use of oxygen, and artificial respiration are shown in detail. The demonstration of the instruments required to deal with this emergency is particularly clear. Cardiac arrest is illustrated in the same manner, its causes are discussed, and a detailed sequence then shows the various forms of treatment. These include the use of stimulant drugs, oxygen, artificial respiration and finally indirect and direct cardiac massage. It is probable that many anaesthetists will think that intra-cardiac adrenaline should be used at an earlier stage than that shown in the film. This is a most valuable teaching film for students and anaesthetists. Emergencies such as these call for quick decision and prompt action, and this film gives the student a clear and vivid plan of the correct course of action so that he will not hesitate when the occasion arises.

A.F.-C.

728/3

SURGERY IN CHEST DISEASE

made by G.B.I., 1943, owned by British Council, 16 mm. sound, 1500 ft. [450 m.], 35 mm. sound, 3780 ft. [1130 m.], 4 reels, black and white, 40 minutes.

The purpose of this film is to indicate the scope and level of thoracic surgery and collateral services in Britain, and most of the film was made at the Brompton Hospital, London. The main case depicted, a man with cancer of the lung, illustrates a striking advance in surgical practice. An industrial worker, in whom an abnormal shadow at the base of one lung is discovered by miniature radiography, is taken into hospital for investigation. There a bronchoscopy is performed and bronchograms are made. Biopsy confirms the diagnosis of bronchial carcinoma. The reasons for the decision to operate are clearly explained. The careful preparation of the patient to enable him to stand the operation is shown, as also the choice and administration of the anaesthetic and the technical details of the operation of pneumonectomy. Stages in recovery are indicated in later sequences, including the treatment of a post-operative pleural effusion. The patient is then shown at

a later stage convalescing at a hospital in the country, where special rehabilitation measures not only aid his recovery, but retrain him for his old job. The film, as a whole, illustrates the growing importance of special techniques and of team-work in modern medicine. This is a film which should be of interest to any medical audience and particularly to audiences of surgeons.

728/4

ACCIDENT SERVICE

made by G.B.I., 1943, owned by British Council, 16 mm. sound, 1440 ft. [430 m.], 35 mm. sound, 3800 ft. [1140 m.], 3 reels, black and white, 40 minutes.

This film depicts the work of an industrial accident service, taking the mining industry, the most hazardous industry in Great Britain, as an example. The film has been made with expert medical advice. All stages in the treatment of severely injured miners are shown and the principles underlying rehabilitation are vividly presented. The lesson of the film is that surgery, after-care, mental, psychological and social welfare, are different aspects of a continuous and co-ordinated process, which has as its ultimate aim, not merely the mending of a broken bone, but the rehabilitation of the whole man. Accident services organized on these lines now exist in many parts of Britain. The object of this film is to show such a service at work. The film should be of interest to orthopaedic surgeons, general medical audiences, senior medical students, nurses and all those concerned in the process whereby an injured man is restored to normal.

728/5

SUBJECT FOR DISCUSSION

made by Seven Leagues Production, Ltd., 1943, owned by Central Council for Health Education, 16 mm. sound, 520 ft. [160 m.], 35 mm. sound, 1312 ft. [390 m.], 2 reels, black and white, 15 minutes.

Before the war, popular knowledge of venereal disease was defective, and the subject was not considered suitable for frank discussion at mixed gatherings. With the increased incidence in venereal diseases that has occurred since the outbreak of the war, such discussion has become essential, so that people should recognize the early manifestations of the diseases and apply for treatment at an earlier and more hopeful stage. The object of this film is to show the sponsoring of such a discussion by the doctor in attendance at a First Aid Post. The resistance to such a discussion is overcome by an account of the possible consequence to the child of unsuspected parental syphilis. The diagnosis and treatment of the parents and of the child are shown. The importance of regular attendance for treatment, even after the disappearance of symptoms, is stressed. The main object of this film was to counter moral objections to the popular ventilation of this subject. It presents a convincing argument and is suitable for exhibition in public cinemas.

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This number on "Skin and its Disorders" is little concerned with that aspect of dermatology which involves the description and classification of skin lesions of uncertain aetiology and only two of the nine special contributions are by dermatologists. A review of the recent interesting work on scabies might have been expected in this number but it has seemed more logical to reserve this subject for publication in the succeeding number, which will be on medical entomology. The articles included provide another example of a tendency—which has been illustrated also in several previous numbers of the Bulletin—for contributions to medical knowledge to be made rather by workers in many different fields than by representatives of a particular "specialty".

The author of the first article, BRIGADIER R. M. B. MACKENNA, received the main part of his medical education at Cambridge University and St Thomas's Hospital, London. For 11 years before the war he was a dermatologist in Liverpool where he joined his father—the late R. W. MacKenna—in consultant practice in 1928. He is honorary dermatologist to the Royal Southern Hospital in that city. From October 1939 he has served in the Royal Army Medical Corps. After 2 years service in the United Kingdom, during which he organized large dermatological and venereal departments and visited many military units, he was promoted and given the appointment of adviser in dermatology in the medical department of the War Office. Under his aegis Army dermatology was divorced from venereology and became a distinct branch of the medical services. In 1944 he was appointed consulting dermatologist to the British Army. During the course of his duties Brigadier MacKenna has made official tours in many theatres of operations, including the Middle East, Iraq, Iran, Italy, Gibraltar, and Northern Europe. In the summer of 1945 he spent 2 months in India, Assam and Burma. His official contacts with many medical representatives of Dominion, Commonwealth and Allied Forces have enabled him to appreciate the dermatological arrangements available in many medical services which have served the Allied Forces in the Field. He has published several papers on dermatological subjects including 'Experiences in military dermatology' (*Brit med J* 1943, 2, 181), and he revised and prepared for publication the 3rd and 4th editions of *Diseases of the skin*, a manual of dermatology originally written by his father, R. W. MacKenna. He has also written a small handbook, *Aids to dermatology*, which is now in its 3rd edition.

DR. J. M. L. BURTENSHAW received his medical education at Oxford and Guy's Hospital, London. During his tenure of the post of assistant bacteriologist at Guy's Hospital he held an Adrian Stokes travelling fellowship, which enabled him to study for 6 months under the late Professor Kolle at the Institut für experimentelle Therapie, Frankfurt-am-Main. He subsequently held posts in the pathological departments of Birmingham University and the Medical School of the University of Wales. He has been first assistant bacteriologist to the Staffordshire County Council since 1940. His work on the self-disinfectant power of the skin was done in Cardiff, in the inoculation department, St Mary's Hospital, London, and in Stafford.

DR. I. MUENDE has been pathologist at St. John's Hospital for Diseases of the Skin for the last 17 years, and is dermatologist to the Middlesex County Council. Originally a pupil of Dr J. M. H. MacLeod, his later postgraduate studies in 1928-29 brought him under the direction of most of the leading authorities in Zürich, Vienna and Paris, and also Padua and Copenhagen. His chief interests in pathology lie in histopathology and mycology. In 1940 he published, together with Dr MacLeod, the 2nd edition of *Practical handbook of the pathology of the skin*, and in 1935 he was given a grant from the Royal College of Physicians over a period of 3 years for the study of the classification of the ringworm fungi. During the past war he has lectured on skin diseases at the London School of Hygiene and Tropical Medicine.

DR. G. WEDDELL is university demonstrator in anatomy at Oxford and is at present a member of the Royal Naval Personnel Research Committee of the Medical Research Council. His researches cover a wide field in medical science, but foremost are his contributions in neurology, and he is the author of a considerable number of original papers on the problems of peripheral innervation. He has also made an extensive study of the electrical activity of voluntary muscle, which has established a place for electromyography in clinical medicine as a diagnostic and prognostic

agent. Dr Weddell spent two years in the U.S.A. as a Fellow of the Commonwealth Fund in 1937. In 1942 he was elected to a Hunterian professorship of the Royal College of Surgeons and in the following year he was awarded the John Hunter medal and the triennial prize (1940-42) of the College for his research work on the ultimate distribution of the sensory peripheral nerves.

DR. A. H. T. ROBB SMITH is Nuffield Reader in pathology in the University of Oxford and director of pathology at the Radcliffe Infirmary, Oxford. He was trained in pathology at St Bartholomew's Hospital under the late Professor E. H. Kettle and while holding a Temple Cross research fellowship, worked with the late Professor Ludwig Aschoff at Freiburg and the late Dr del Rio Hortega in Madrid. For the last ten years he has made a special study of the morphological pathology of diseases of the blood and blood forming organs and since 1938 with the aid of a grant from the Lady Tata Foundation, he has established the Oxford Lymph Node Registry, to which tissues from cases of primary lymph node disease may be sent for opinion and recording. A review of the follow-up of a thousand cases during the last 6 years was presented to the Faculty of Radiologists in the Skinner Lecture of 1944, and will shortly be published. During the war, Dr Robb-Smith has been investigating the morbid anatomy of certain traumatic conditions—fat embolism, acute anoxia, gas gangrene and "shock". Although a morbid histologist by experience, he is a strong believer in the integration of the four branches of diagnostic pathology—bacteriology, biochemistry, haematology and histology and in the application of the experimental method to the elucidation of clinical pathological problems.

DR. W. S. S. LADELL is at present working with the Heat Research Team of the Medical Research Council, under Dr E. A. Carmichael, at the National Hospital, Queen Square, London. He graduated at Cambridge University and worked for a time at the Strangeways Research Laboratory, and for the British Empire Cancer Campaign. In 1935 he went to the physiology department of the University of Cape Town, S. Africa, where he was teaching for 6 years. During this time he was doing research in tissue-culture. He returned to England in 1941, and began working for the Medical Research Council on problems connected with the saving of life at sea after shipwreck, with particular reference to water and salt requirements. In 1943 he went to Iraq with Dr J. C. Waterlow to investigate, for the British Army casualties caused by heat. Since his return from Iraq he has been investigating the physiological effects of exposure to tropical climates, with particular reference to military requirements.

DR. B. S. PLATT has previously contributed to the Bulletin, and a note on his work appeared in No. 10-11 of Volume 2.

PROFESSOR H. BERRY, holds the chair of Pharmaceutics in the University of London, and is also dean of the College of the Pharmaceutical Society, a member of the British Pharmacopoeia Commission, and an examiner in pharmacy for the universities of London, Glasgow, Manchester and Wales. His published research work includes papers on the bactericidal activities of acridine derivatives and of the ethers of ethyleneglycol, and on the stability of strophanthin K. He is also the author of several papers concerned with the problems arising from the sterilization of preparation for parenteral injection, and was a member of the Medical Research Council's Committee on the Sterilization of Syringes, whose recently published report is reviewed (*BMB* 773/158) in this number.

DR. ELIOT SLATER received his medical education at Cambridge and St George's Hospital, London. Since 1931 he has been associated with the Maudsley Hospital and learned psychiatry under the stimulating influence of the late Prof. E. Mapother. He became interested in constitutional and genetical aspects of psychiatry during the tenure of a Rockefeller research fellowship in Germany in 1934-35 and most of his work since has been in that field, and in the physical aspects of nervous and mental disorders. In 1938 he was awarded the Gaskell gold medal of the Royal Medico-Psychological Association. During the war he has been clinical director of the neuro-psychiatric unit of an Emergency Medical Service Hospital concerned with the rehabilitation of neurotic soldiers. He believes that the future of psychiatry lies in its integration with general medicine.

REVIEW OF SELECTED PAPERS. Contributions to this section have been received from Lt.-Col. J. W. Bigger, Dr E. Lipman Cohen, Dr D. Erskine, Dr A. W. Fergusson, Dr F. Hawking, Dr M. Johnson, Dr R. Klüber, Dr A. C. Roxburgh, Dr E. W. Prosser Thomas and Prof. B. W. Windeyer.

ON MILITARY DERMATOLOGY

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In many military forces and groups, special provision is not made for dermatological cases; in some armies dermatologists are available to deal with syphilis and cutaneous disease, in the British Army, dermatology has achieved the status of an independent speciality which, although closely integrated with the work of other branches of medicine, has acquired an individual status of its own.

In this essay military dermatology will be discussed in the light of the author's experience in the British Army. Obviously the first matter which must be decided is whether the incidence of skin diseases in a modern army justifies the provision of a special dermatological service.

Incidence of Skin Disease in the Army

In the South African War (1899-1902), skin diseases were found to be one of the principal causes of inefficiency in the British Army, during this campaign the average annual incidence of skin diseases per thousand troops was 23.71, a number approximately equivalent to half the battle casualties. In the war of 1914-1918, skin diseases again became notorious because of the wastage by sickness that they caused. In 1915, in the United Kingdom, 40.88 men in every thousand were admitted to hospital because of diseases of the skin and areolar tissue, in France and Flanders in the same year the ratio among British troops was 126.13 in every thousand. Therefore it is not surprising to learn that throughout the recent hostilities the incidence of skin disease has been relatively high in all theatres of war. Statistics concerning this incidence are, of course, available, unfortunately they cannot be published. An indication of the morbidity-rate in the British Army from cutaneous diseases during the years 1940-1945 may be gained by stating that in most theatres of operations, except those in which there are special hazards, it has been advisable to arrange that 10% of the total beds available for sick personnel should be set aside for dermatological purposes. It will be noted that beds available for battle casualties are not included in this assessment. There is no evidence to indicate that the incidence of skin diseases is higher among the personnel of the British Army than among the personnel of other armies, neither is there any evidence to suggest that troops are necessarily more prone to skin diseases than the civilian population of any given area, in many instances the reverse is true. Armies appear to suffer greatly from cutaneous diseases, but if in the civilian populations comparable statistics were kept, if every case of scabies was notified, every case of impetigo hospitalized, and every case of psoriasis separately assessed, dermatology would loom as large in the civilian sphere as it does in the military.

Organization of a Dermatological Service

In war, the factors of fundamental importance are man-power, equipment, mobility and generalship. The medical services of an army are vitally concerned with the first of these, they must prevent wastage of man-power, first by prosecuting all possible measures for the prevention of disease, secondly by arranging that the sick are treated as skilfully and expeditiously as possible, so that the maximum number of patients is rendered fit for duty within the shortest possible time and only a minimal number re-categorized as "permanently unfit for military service" and returned to civilian life. An efficient dermatological service, formed within the framework of the medical services of an army, must be organized in accordance with these principles.

It is important to realize that usually the greatest hazard to which the patient who is suffering from a cutaneous disease is exposed during the first stages of his malady is that he is treated by a unit (regimental) medical officer who, as he has had no specialized training in dermatology, may be uncertain of the diagnosis, and therefore may conduct treatment by a

method of trial and error. This method is successful only in a few cases. In the majority it leads to an aggravation of the disability, the development of complications such as secondary infection or dermatitis medicamentosa, and eventually to an unnecessarily prolonged period of hospitalization. Therefore a fundamental part of the policy to be adopted in organizing a dermatological service must be that fully equipped centres, each under the aegis of a trained dermatologist, must be available, and that evacuation of cases to these centres must be rapidly achieved. Further, in each corps a dermatologist should be available whose activities must not be entirely confined to work in a skin clinic. He must have authority to travel about the corps area and to instruct unit medical officers on the prevention, diagnosis and treatment of cutaneous diseases. Arrangements should be made whereby certain maladies, e.g. scabies, can be diagnosed and treated in units (i.e. in the regiments concerned), the corps dermatologist must be available generally to supervise this work, and to ensure that proper standards of diagnosis and therapy are maintained.

On the staff of the Director of Medical Services of each Army there should be an Adviser or Consultant in Dermatology, an officer of great professional competence who possesses administrative ability, such officers are not easily discovered. Each corps dermatologist should be responsible to the Adviser or Consultant for the efficiency of the clinical services for which he is responsible. The Adviser or Consultant must himself be in contact with and subordinate to the dermatological authorities in the Department of State for War.

These, briefly, are the lines on which a successful organization for a dermatological service can be planned, a great amount of data could be added, but as the reader is probably more interested in clinical matters than in details of administration, we will now consider some of the preventive measures which are of importance in military dermatology.

In the organization of a dermatological service for an army, the preventive measures must commence before the candidates for military service are embodied. Thus, the medical boards who examine candidates for military service must be fully cognizant of the hazards presented by cutaneous diseases, so that men and women suffering from maladies which will be rapidly and gravely aggravated by active service, are not allowed to proceed to enlistment. In some cases, e.g., those of persons manifesting symptoms of cutaneous tuberculosis, decisions are easily reached. In cases of pompholyx, eczema and psoriasis the assessment may be a matter of difficulty.

Military Disposal of Men with Skin Disease

It is important that, when embodied, the recruit is rapidly and correctly classified medically, so that if he suffers from a skin disease he may be usefully employed within the limits of his physical disability. For example, a man with severe acne of the back can be usefully trained for duties as a driver or clerk, but he would rapidly fall sick if plunged into heavy infantry training in which he would have to carry a pack on his back. It may be true that a patient with psoriasis usually benefits from exposure to ultra-violet rays, but heat, sweating and friction will more than nullify any beneficial effect that accrues from exposure to these rays, therefore many psoriatics do badly during military service in hot countries, and are best classified medically so that they are retained for duties in temperate climates. On the other hand, men suffering from mild degrees of ichthyosis usually keep more fit in hot countries than in cold.

The subject of the military classification of men suffering from cutaneous diseases is one to which much space might be devoted. During the war the United Kingdom has been pressed to the utmost limits not only to find fit men for duty,

but also to make the fullest possible use of men suffering from chronic disabilities, because of this we have insisted that all military dermatologists should regard the assessment of these cases as being a matter of vital importance, and we have not regarded dermatologists as competent if their judgment has been faulty in this respect

Preventive Dermatology

In its wider aspects preventive dermatology is concerned with many matters, e.g. with the provision of adequate washing and laundering facilities. These facilities are also the concern of combatant officers, hygiene officers and personnel of medical, engineering and service corps, all of whom are alert to ensure that as many mobile field-laundries and mobile bath-units are available as service conditions allow. The provision of soap, and the types of soap to be used for washing, shaving, and laundering in hard, brackish and salt water, are matters which those interested in dermatology must study. Matters concerning nutrition are also within their purview. Further, military dermatologists must be prepared to be consulted about hazards which, in civilian practice, are not likely to be met. For example, assault troops often darken the skin of their faces, necks and hands for purposes of camouflage. Innumerable substances, ranging from cocoa to cow-dung, have been used for this purpose, the provision of suitable staining creams which will give an adequate depth of colour but which will not wash off or sweat out for long periods, which will not interfere with the mechanism of heat regulation of the skin, and which will not permanently stain the integument, or cause dermatitis, is an example of the type of problem in preventive medicine concerning which the dermatologist, in association with chemists and physiologists, may be called upon to give an authoritative opinion.

The military dermatologist must also know much about the prevention of occupational dermatitis, for there are many duties performed daily by certain military personnel which involve long-continued exposure to deleterious dusts and liquids. The prevention of this form of contact dermatitis is a matter which comes under the purview of senior military dermatologists and may eventually demand the establishment of a special section of dermatologists and biochemists.

The military dermatologist must be a man of patience, who is prepared to see his best-planned schemes fail because of the exigencies of the service. Thus, during the campaign in the Libyan Desert, the so-called Desert Sore—a lesion which appears to have been an indolent type of ecthyma—occurred principally after slight trauma of exposed areas where the skin had been devitalized by exposure to heat, winds and dust. These desert sores caused much personal discomfort and sick-wastage. A large-scale experiment was being launched by the dermatologists and hygiene officers to determine whether the provision of a suitable emollient cream would counteract the effects of wind, sun and dust, but events moved too swiftly, and the great victory of El Alamein, and the swift advances of our troops, nullified the experiment and served to point another moral for the military student of dermatology.

Special Considerations

Having briefly considered these matters with regard to the prevention of cutaneous diseases, we may now enumerate several special considerations which influence the practice of military dermatology, thereafter mention will be made of the cutaneous maladies which are of maximal importance to military dermatologists, and these important diseases will then be discussed in the light of the special considerations which are adumbrated.

i. A military dermatologist must be prepared to carry his rank as an officer as well as use his ability as a doctor. Many clinicians when they join an army say quite openly that although they must wear a uniform they do not wish to assume the bearing of an officer and that they do not wish to become militarized. Usually they find quickly that their patients are at a loss as to how to regard them and learn that their attitude is based on false premises. Eventually the best men in any group of medical specialists are reasonably military in their bearing and outlook.

ii. Speed in therapy is of paramount importance in order to achieve the necessary rapidity, cases must from the outset be correctly diagnosed and rapidly assessed. New methods

of therapy which give more speedy results than routine measures must be rapidly incorporated into military practice.

iii. For the last-stated reason the senior dermatologists in the army must have the broadest contacts with scientists and clinicians, and must have facilities to prosecute relevant research. They should be aware of the research work which is being undertaken in their own subject, and also of that which is proceeding along parallel channels in other branches of science and medicine.

iv. As a corollary, these senior dermatologists must have ability in assessing recent advances in medicine and must be able to impart their knowledge to others.

v. The clinician must be prepared to appreciate the difficulties of the administrator, and be willing to co-operate to relieve these difficulties whenever possible.

vi. Dermatologists must be available to supervise the rehabilitation of men who have suffered severely from skin diseases.

In certain geographical areas, there are endemic diseases which are not prevalent elsewhere. The desert sore has already been mentioned and may be taken as one example, cutaneous leishmaniasis, prickly heat, and tinea imbricata, are three other examples which come to mind. These "geographical diseases" (if they may be so called) are not of major importance to the dermatologist. There are other more prevalent maladies which are seen in white and in coloured troops in all parts of the world. In hot countries these diseases are aggravated by sweating and their diagnosis is difficult, for the clinical picture frequently is masked by the heavy pigmentation of the skins of the patients. The military dermatologist must have a very wide knowledge of these diseases. Placed in order of importance they are

1 Parasitic diseases

a Pediculosis

b Scabies

2. Impetigo contagiosa and allied eruptions, e.g. ecthyma, staphylo-streptoderma, infectious eczematoid dermatitis, etc

3. Seborrhoic dermatitis

4. Eczema and also sensitization eruptions of exogenous origin.

5. Pompholyx

6. Tinea

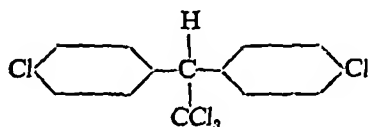
Provided that an army is in the field and is not living in intimate contact with an uncontrolled civilian population, and also is not rapidly over-running a heavily infested enemy, parasitic diseases should, by modern methods, be kept under control. This is of great importance for, as is well known, lice are vectors of typhus, relapsing fever and trench fever, all of these being maladies which are of vital importance to armies, also, as was noted particularly during the war of 1914-1918, septic dermatoses are frequent complications of pediculosis and cause much sick-wastage.

DDT and Louse-control

The introduction of DDT to control infestations is a milestone in military history—a digression concerning this compound may perhaps be pardoned, for the story of DDT illustrates vividly one of the axioms of military practice, viz., that the hygienists and clinicians must ever be on the alert to note new discoveries, ready rapidly to assess the value of new or recently-introduced therapeutic agents and promptly to include more effective weapons in their therapeutic armamentarium.

In the early years of the recent war the British Army depended for insecticides mainly on pyrethrum and derris root. The entry of Japan into the war and the occupation of Malaya deprived us of half our pyrethrum supplies and nearly all our derris. In 1942 the pyrethrum crop in Kenya was a poor one, even the normal crop was barely enough to supply the fighting services of the Allies, and would have left no margin for agricultural purposes and for the preservation of stored food. Fortunately in that year the British military attaché at Geneva called the attention of our Government to DDT, and research into the possibilities of this chemical as an insecticide was immediately begun. We learned that DDT had originally been discovered in 1874, but its potentialities had not been investigated until 1939 when Messrs J. R. Geigy, of Basle, Switzerland, had found that it was an excellent insecticide against moths and bed-bugs.

The initials DDT stand for dichlor-diphenyl-trichlor-ethane, and the graphic formula of the compound is stated to be



The use of DDT, both as an impregnant of clothes to proof them against lice, and in powder form as a protective and curative agent, has proved its worth. It is worth noting that even before the introduction of DDT, the standard of hygiene of the British Army was so high that pediculosis seldom caused anxiety, but, since the introduction of DDT, never in the history of European warfare have armies been so free from lice as the Allied Armies in France, Germany and Italy. The story of the control of typhus in Naples in 1943 has often been told, the story of the control of typhus in the concentration camps and elsewhere in Germany during the terminal phases of the recent war has yet to be written. It is one of the unexplained mysteries of the war why the German General Staff failed to realize the importance of the work done by the Geigy Company, who were manufacturing their product in a country contiguous with Germany, particularly as throughout the period of hostilities a relatively high percentage of German troops, when taken prisoner, were found to be infested with lice.

Scabies

The clinicians of the medical services of an army should always be prepared to co-operate in ameliorating the difficulties experienced by the administrative branches. An illustration of this precept is given by the following brief consideration of the scabies problem. Scabies is endemic, and the incidence in Europe and Asia seems to have been greater during the past 10 years than during many previous decades. The infestation cannot easily be eradicated from an army which is living in close contact with a civilian population. During the early years of the war, when we had to build a large army in the United Kingdom, the incidence of scabies in the Army caused much difficulty. On the administrative side the need to provide transport to move the cases from their units to scabies centres, the deterioration of bedding and clothing caused by steam disinfection, the heavy cost of maintaining and staffing scabies centres, and the necessarily lavish provision of hot water and bathing facilities were all sources of complaint. The introduction of benzyl benzoate emulsion as a standard remedy obviated all these disadvantages, for when this emulsion is used, the patient is treated at his unit and is not off duty for more than an hour because of his malady, routine disinfection of clothing and bedding is no longer necessary, and, finally, the application of the emulsion need not be preceded nor followed by baths, thus the provision of elaborate scabies centres is now unnecessary and in the majority of units, at least 95 % of cases are cured after two applications of the remedy.

Other Skin Hazards

Impetigo and allied eruptions are always troublesome but a consideration of these maladies need not detain us here. Eczema and sensitization-eruptions of exogenous origin are an ever-increasing hazard, as the science of chemistry is increasingly applied to the art of war, so proportionately are the hazards of sensitization eruptions incurred. The impregnation of clothing against vesicant gases, the wearing of rubber respirator face-pieces, the impregnation of textiles, canvas, cordage, and many other items of equipment with "rot-proofing chemicals" designed to prevent the invasion of botanical and zoological parasites (fungi, white ants, etc.), the introduction of chlorinated naphthalenes as electrical insulating agents—these and scores of other hazards which are steadily increasing in number all add to the cutaneous risks of the combatant and demand specialized knowledge from those responsible for his freedom from disease, as well as those responsible for his care in illness.

Tinea and pompholyx have both received mention, perhaps it is worth noting that there is good evidence to believe that tinea pedis is much less common than frequently is supposed, of 100 cases diagnosed by the average general practitioner or unit medical officer, only ten will be found

in an average sample to be true examples of this malady; the majority of the remainder are cases of pompholyx or are due to maceration and pyogenic infection of the skin. In an army, pompholyx is often psychosomatic in origin. We have noted that tinea cruris is relatively common among males, but is rarely reported from women's units.

Importance of Prognosis

Besides a highly cultivated ability to deal with the protean manifestations of the cutaneous diseases commonly seen in military practice, the military dermatologist must always assess his patients as fully as possible as soon as they come under his care. This assessment is of the utmost importance. Briefly, it consists in estimating the probable duration of their diseases, determining the prospects with regard to recurrence after apparent cure, and deciding the lines of therapy which will ensure that the patient recovers in the minimum time. It is necessary to know the probable duration of the disease because, if the patient will require a long period of hospitalization, he will best be transferred to a base hospital or evacuated to his home country. A knowledge of the probability of relapse occurring soon after apparent cure will again affect the policy of the forward holding units. A patient who is cured when he leaves hospital is an asset, the patient who leaves hospital with the probability of suffering a relapse within the ensuing month or six weeks is a liability for which the medical services must make provision. Often such a case is best evacuated from a forward area.

Speed of Treatment

Speed of therapy is of great importance. The sooner a man is discharged from hospital, the sooner he is of value to the Army Commander. Further, however military is the atmosphere of a hospital, a man's worth as a soldier deteriorates proportionately with his length of stay in the wards. A man who is in hospital for only a few days can usually be returned to his unit for duty. A man who has been in hospital for a few weeks must pass through a convalescent depot and a holding battalion before he is hardened sufficiently to return to active duties. The longer he is in hospital, the more time has to be spent, medical personnel made available, and special facilities arranged to rehabilitate him for active service.

We welcomed penicillin (which in our dermatological therapy is usually applied several times daily as a spray containing 200–1,000 units per cm²), for the use of this antibiotic has the great advantage of being the most rapid therapy yet invented for impetigo contagiosa. Previously we had investigated the claim of Harris (1943) that micro-crystalline sulphathiazole was an extremely rapid form of therapy for this malady. Our findings were that this was a speedy method of treatment but carried a hazard of sensitization in some 2 % of cases.

Maintaining Contact with New Developments

It is essential that those responsible for the efficiency of the dermatological services of an army should be aware of research which is proceeding on parallel lines to their own, and which may have applications to their special field. For example, the introduction of a compound—the formula for which is still on the secret list—for the treatment of vesicant-gas injuries was followed by an investigation of its possibilities when used for more mundane maladies and, as a result, the treatment of exfoliative dermatitis due to neoarsphenamine has been revolutionized, the cures obtained are often dramatic in their swiftness, a fact which is appreciated both by the patients and their officers.

This reference to knowledge of parallel research emphasizes the importance, in the scheme of the administration of a dermatological service, of an officer or officers who are fully trained dermatologists and who are to some degree—but not entirely—emancipated from routine clinical work. These must be men who have sufficient time to study the world literature of their subject, and have sufficient knowledge to evaluate and assess new propositions in clinical methods and in therapy—with sufficient background to be able to make and maintain the broadest contacts amongst scientists and clinicians, and sufficient ability to teach by the four methods of precept, verbal instruction, admonition and example. These officers must be able to conduct courses of instruction, visit hospitals at home and abroad, and ensure

that a high standard of dermatology is being maintained, that new knowledge is disseminated to all dermatologists, however remote their location, and that improvements in the service which originate in one area are rapidly adopted in other theatres of operations

Conclusion

During the stress of war, the motives and mechanisms of the human mind are revealed to a greater degree than during the quieter years of peace. Those responsible for the efficiency of a dermatological service must watch two points that, in clinical work, due regard is paid to psychosomatic factors and, conversely, that the less experienced clinicians do not become obsessed with psychological theories which are more plausible than accurate and which lead to an exaggerated value being placed on the psychological factors of diseases at the expense of the somatic factors.

Finally, in this brief summary of dermatology from the military aspect, mention must be made of the rehabilitation of patients suffering from cutaneous diseases. In any scheme of rehabilitation the psychiatric aspects are of paramount importance. They have been discussed fully by Miller (1945) who has devoted some part of his paper to dermatological conditions and who defines "rehabilitation" as "a planned

method of treatment, designed progressively to mobilize all the available resources of the patient, with a view to his most complete adjustment to social and economic needs." Rehabilitation must not be regarded as the prerogative of the orthopaedic patient, men suffering from cutaneous diseases also must be won from treatment to vocational activity, thence to functional practice, and, further, to that stage of fighting fitness which can be promptly achieved only as the result of full therapeutic co-operation. We believe that in the British Army we have achieved the first steps in discovering a method of rehabilitation of skin diseases which not only may form the foundation for further advance in this matter, but which prevents the wastage of many men from the Army, these men, if given only the facilities for hospital treatment, would not have been restored sufficiently to health for further active service.

The task of the military dermatologist is not easy, but his duties are of wide range and considerable interest. He has two main objectives which he must ever strive to attain. These are to prevent disease whenever possible, and when disease has developed, to heal his patients quickly, safely, and with that kindness and understanding which must ever exist between officers and men—combatant and non-combatant—of an efficient fighting service.

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SELF-DISINFECTION OF THE SKIN A SHORT REVIEW AND SOME ORIGINAL OBSERVATIONS

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Before the discovery of the role of micro-organisms in disease, the skin was regarded as a membrane bounding the body and affording some mechanical protection. Sabouraud (1899) seems to have been the first author to form a picture of the manner whereby the skin rids itself of bacteria. He says "La vie même de l'épiderme, sa vie normale, amène incessamment ses couches profondes à la surface, où elles s'exfolient. Il se produit donc une perpétuelle exfoliation des couches mortifiées, et, si elles sont microbiennes, une perpétuelle éviction des microbes qui vivent sur elles." In brief, micro-organisms on the skin's surface, being unable to invade except by proliferation, are eliminated by the gradual approach of successive layers of the epidermis to the surface and their desquamation. Metchnikoff (1901) agrees with this view, but naturally does not fail to stress the engulfing activities of the phagocytes, not only in the dermis but also in the epidermal rete mucosum and stratum granulosum. Koch (1908), Zangemeister (1910), and Grütz (1912) concur in the view that haemolytic streptococci and other pathogenic organisms are only rarely cultured from skin, except from that of persons constantly exposed to them, such as midwives and patients suffering from infected and open lesions. It is convenient to divide the process of removal of bacteria from the skin into two stages: disinfection on the skin's surface and disinfection in the skin.

1 Disinfection in the Depths of the Skin

The well-known processes of inflammation and humoral immunity operate defensively in the skin as in every other tissue. Many attempts have been made to determine whether the skin can develop an active immunity, either specific or non-specific, independent of humoral immunity shared with the other tissues. The work of Meierowitsch (1888), Cobbett & Melsome (1895), Rivers (1925) and Amoss & Bliss (1927) shows that localized immunity can be conferred by previous infection of a skin-area with streptococci, but that immunity over the whole skin is only acquired concurrently with generalized humoral immunity. What is the mechanism of this local immunity? Cobbett & Melsome (1898) and Mallory & Marble (1925) proved that the injection of bacterial filtrates, mustard oil, or broth into an area of skin protects that area against streptococcal infection as effectively as

an injection of dead streptococci. The histological work of Freedlander & Toomey (1928) revealed how the inflammatory response to injected staphylococci was facilitated and perfected by previous application of broth-compresses. It appears that the increased local resistance of the skin, after antecedent infection and inflammation, to subsequent infection is largely non-specific and due to a more efficient inflammatory process.

2 Disinfection on the Skin Surface

Dold & Chen Yü Hsiang (1919) pointed out that drying certainly, and exposure to light probably, contribute to destruction of organisms on the skin, and that the innumerable irregularities of the skin-surface, by trapping but not killing deposited organisms, may give an erroneous impression of the skin's disinfectant power. Marchionni and his colleagues in a series of papers (Schade & Marchionni, 1928a, 1928b; Marchionni & Cerutti, 1932; Marchionni, 1939) adduced much evidence that the sterilizing power of different areas of skin depends upon, or varies with, their degree of acidity. Many workers, notably Singer & Arnold (1929), Colebrook (1930), Karns & Arnold (1931), Cornbleet & Montgomery (1931), Bryan & Mallman (1933), using various organisms, such as staphylococci, streptococci, *Erythrobacillus prodigiosus*, *Bact. coli*, concluded that, in addition to desiccation, some other factor contributed to destroy bacteria on the skin, and Arnold & Bart (1934) observed that this factor was enhanced by putting subjects on a ketogenic diet. Cornbleet (1932a, 1932b) contested the view of Marchionni that self-disinfection depends upon the acidity of sweat. He and Hermann & Fürst (1929) claimed cure of skin-infections by sweat baths, even when the sweat was alkaline. Norton & Novy (1931, 1932) asserted that desiccation alone accounted for death of organisms on the skin, which had no specific bactericidal power.

Recently Arnold (1942) has argued that the horny skin behaves like a gel. On acidification it contracts, imprisoning the endogenous flora, whilst the increased H⁺ ion destroys any surface organisms. On alkalinization it absorbs water, becoming more porous and allowing imprisoned bacteria to escape to the surface. Again, Bergeim & Cornbleet (1943) are satisfied that the lactic and volatile fatty acids of sweat,

by reason of their acidity and perhaps of some specific action, exert a mild antiseptic action on the skin

It seems then that the following factors are important in removal of micro-organisms from the skin surface (i) Desquamation and certain physical properties of the epidermis (ii) Desiccation (iii) Acidity of the skin (iv) Fatty acids (v) Certain ill-defined bactericidal agents Factors iii, iv, and v may be considered further

3 The pH of the Skin and of the Sweat and the Substances producing it

In 1848 Andral remarked "Quelles que soient les conditions de santé ou de maladie dans lesquelles j'ai examiné la sueur, je l'ai trouvée le plus ordinairement acide, quelquefois neutre, et jamais alcaline"

Most later work has demonstrated the acidity of human sweat, which may after long-continued secretion become more alkaline through progressive dilution For example, Talbert (1919), using both indicators and the hydrogen electrode, proved that work- and heat-sweat had a pH of 5.22-6.63, and Marchionini (1928) determined the reactions of the skin and sweat by electrometric methods and found them to be about pH 3.8 and pH 3.8-5.6 respectively over most parts of the body Exceptional areas were the axillae and perineum, supplied by apocrine glands, whose sweat had a pH of 6.2-6.9, and parts such as the forehead, naso-labial folds, and interdigital regions, which, though supplied with eccrine glands, became more alkaline at puberty He accounted for the skin being more acid than sweat by invoking the concentration of sweat by evaporation from the skin In later papers Marchionini & Hausknecht (1938) and Marchionini (1939) delineate more exactly the "gaps in the acid mantle" of the skin and demonstrate that atrophic lesions, scurf- and blister-producing processes (psoriasis, eczema, etc.) and chronic inflammations (acne vulgaris) lead to increased alkalinity (pH 8.3-5.8), whilst the blister-fluid in true dyshydrosis and the pus of acute inflammation (boils) is acid (pH 5.8-4.8) The work of Pillsbury & Shaffer (1939) confirms the regional differences of skin reaction discovered by Marchionini In short, the

over most of the body surface is normally acid, and the sweat and perhaps the sebum produces this acidity

What are the substances forming part of, or excreted through, the skin, which confer upon it acidity?

Many authors, for example Aubert (1872), Rohrig (1872), Fubini & Ronchi (1881), Schierbeck (1893), have noted the excretion in sweat of CO_2 and queried its possible effect on the skin pH In Talbert's experiments (1919) any CO_2 in sweat was certainly not responsible for the observed acidity, because equalization of gas-pressures between air and sweat was allowed before pH estimations were carried out According to Unna & Golodetz (1909) sebum fat, sweat-gland fat from the soles, and fat from the horny layer of the epidermis contain about 50% of fatty acids of high molecular weight, and Unna (1913) recorded that lactic and the volatile fatty acids, from formic to caproic, are present in sweat In a review of the skin secretions Schwenkerbecher (1929) states that lactic acid, with the help of other acids such as the volatile fatty acids from formic to caprylic, derived probably from decomposed sebum, is mainly responsible for the reaction of sweat From the work of these authors and many others, such as Fishberg & Bierman (1932), McSwiney (1934), Couraud (1935), it seems that the substances responsible for skin acidity are lactic acid and fatty acids of the acetic series

4 Other Bactericidal Factors operating on the Skin

Ever since Hippocrates there has been a periodic revival of interest in the possible existence of a poisonous substance emanating from the skin of menstruating women Such a substance, supposed to be not only bactericidal, but to cause flowers to wilt and fermentation processes to alter their course, was described by Schuck (1920) and named by him "menotoxin" He ends his paper on a note of triumph "Ich aber sage, wir sollen uns freuen, dass dieser Glaube nicht ausgerottet ist, wir sollen dem Volke dankbar sein, dass es an solchen durch mündliche Überlieferung fortlebenden Tatsachen zähe festhält" This enthusiastic vindication of folklore has not been upheld by others Neither Sanger (1921) nor Gengenbach (1925) could support it, and Rothman (1929) remarks that menotoxin is a myth

Fleming (1922) described a substance, called by him "lysozyme", present in varying amount in most animal tissues including the skin It is lytic in high dilution to a coccus recovered from the nose, *Micrococcus lysodeiktilus*, but it is also active against many other organisms

Brann (1928) drew attention to the sterilizing effect of ether- and acetone-extracts of hair and skin of man and animals, and his discovery was extended by the research of Stevens (1937), who revealed that the lipoids of guinea pig skin take up oxygen, which is available in an active form and can be estimated by the oxidation of ferrous iron to ferric This active oxygen is produced in the dark, but its quantity is increased by exposure of the skin or of its extracted lipoids to ultra-violet radiation Organisms, especially the haemolytic streptococcus, are killed, or their growth is inhibited, by volatile peroxides given off by the irradiated lipoids, and both the active oxygen and the bactericidal power of the lipoids are annulled by reduction with cysteine No experiments were done with the fats of human skin, but it is likely that these fats may behave similarly

Cornbleet (1933), as well as Bryan & Mallman (1933), recorded increase in the sterilizing power of skin after exposure to sunlight, whilst Marchionini & Schmidt (1939) observed that ultra-violet radiation induced a temporary heightening of skin acidity, which may partially explain the more rapid death of organisms on irradiated skin

It may be concluded that, of possible bactericidal agents operating on the skin other than those enumerated in Section 2, i-iii, menotoxin may conceivably exist, but is extremely rare, ultra-violet radiation, apart from direct destructive action, also disinfects by increasing skin acidity, while lysozyme and lipoids may play a role, which is assessed in a later section

5. Original Observations on the Self-Disinfection of the Skin

In a preliminary investigation (Burtenshaw, 1938) I devised a new technique for removing organisms from the skin and other surfaces Streptococci or staphylococci suspended in normal saline or distilled water were spread over a previously demarcated area of skin on the hand or forearm, or of a control surface, such as dead skin, glass, or rubber A shallow glass cylinder was clamped by means of a brass frame and elastic bands over the organism-coated area, a definite quantity of saline was then introduced, at various intervals after evaporation of the water, and the deposited organisms were scraped off into it with the end of a glass slide

The saline was then withdrawn by pipette, an aliquot part of it was incorporated in a blood-agar plate, and the colonies were counted after incubation with the aid of a Pake's disc over an illuminated counting box Similar experiments were made on the skin of the finger-tips, from which the deposited organisms were washed off into saline in a shallow bath I concluded that the skin-surfaces examined could be arranged in a descending order of disinfectant power to the streptococcus as follows palms, finger-tips, forearm By contrast, the strain of *Staph aureus* used was not more affected by exposure on living than on dead skin, and was less affected by exposure on skin than by exposure on rubber sheeting or tinfoil I argued that there might be correlation between the degree of acidity of the skin and its power to kill the haemolytic streptococcus, and expressed the opinion that "some areas of the skin exert a disinfectant action by virtue of their secretion of sweat"

In a later study (Burtenshaw, 1942) I prepared suspensions of skin particles in saline, using the same cylinder and frame, and discovered that *Strept pyogenes* added to these suspensions died far more rapidly than when added to saline alone or to saline suspensions of talc Furthermore, the ratio of mortality in skin-suspensions to that in talc-suspensions was increased with reduction of pH over the range of 7.0-4.0 Usually the pH of suspensions from the palm was initially between 4.0-5.0, a finding which confirms Marchionini's statements about the reaction of the human skin

As a result of the work of Brann (1928), I prepared ether-extracts, suspended in saline, not only of skin, but also of human hair, nails and cerumen, and tested them for their power to kill streptococci and a number of other organisms Such extracts were far more lethal than saline extracts to *Strept pyogenes* and *Strept viridans* Their bactericidal effect on *C diphtheriae* was pronounced and constant, on

Strept pneumoniae and *Staph aureus* and *Staph epidermidis* inconstant, and on *Bact typhosum* and *Bact coli* absent

Ether-extract from hair was analyzed by ordinary chemical methods, and the different fractions were examined for streptococcicidal power. Only fractions containing fatty acids and soaps were active. Fractions containing esters of fatty acids, sterols, and higher alcohols were inactive. A number of fatty acids prepared by British Drug Houses, Ltd and the fatty acids of butter were tested for streptococcicidal power. Only the acids with longer chains, capric, lauric, oleic and stearic and, less actively, their soaps, killed the streptococcus. The unsaturated oleic was more active than its saturated homologue, stearic acid. Certain other substances found in the skin and its secretions, such as lactic, citric and ascorbic acids, were tested against *Strept pyogenes*, they were all inactive. Ether-extracts and fatty acids were always tested at a nearly neutral (pH 7.0-8.0) and at an acid (about pH 4.5) reaction, the more-acid suspension was the better bactericide.

To confirm the work of Wrenn (1927), Stevens (1935, 1936), and others, I tested the effect of cysteine on ether-extracts of skin, hair, etc., and on fatty acids. These experiments are discussed in Section 6.

A few experiments were done bearing on the possible relationship of the sterilizing substance in skin and hair to Fleming's lysozyme. Enough of a saline suspension of a haemolytic streptococcus was incorporated in blood-agar plates to produce on incubation a just-countable number of colonies. Holes about 5 mm in diameter were punched out of the set agar and filled with saline suspensions of actively streptococcicidal ether-extract of hair, and also with control substances such as butter, vaseline, paraffin wax and olive oil. There was no sign of inhibition of growth immediately round any of the implanted substances. The inference from this observation is that the sterilizing substance in hair-fat cannot diffuse in a watery medium. Other experiments on the relationship of hair- and skin-fats to lysozyme are referred to in Section 6.

6 Discussion

It emerges from the foregoing work that there are present in the skin, its appendages and its secretions, lipoids lethal to *Strept pyogenes* and *Strept viridans* and to certain other organisms. Fatty acids are the active constituent of hair-fat, and it may be assumed that these substances endow the other skin fats with disinfectant power. That these acids have long chains is supported by their low volatility, high ether-water repartition ratio, and the proved bactericidal power of commonly occurring long-chain acids and soaps.

My demonstration of the susceptibility of the streptococcus to oleic, stearic, lauric, and capric acids and their soaps, and of its resistance to the lower fatty acids and soaps, harmonizes with the observations of many workers, notably Lamar (1911), Walker (1924), Eggerth (1926) and Bayliss (1936). I found *C diphtheriae* sensitive, and *Staph aureus* insensitive, to hair-fats. Walker (1925) noted the extreme sensitiveness of *C diphtheriae* to oleates, and both Walker and Bayliss pointed out the relative insensitiveness of the group *Bacterium* and of *Staph aureus* to long-chain acids and soaps, though *Bact coli* is affected by high concentrations (1%) of the long-chain saturated soaps. The parallelism between the sterilizing ability of the long-chain fatty acids, such as lauric, oleic, stearic, and their soaps, and that of the fatty acid moiety of hair-fats, allows the inference that these or similar acids are the active components in these fats. That the whole range of fatty acids from formic to oleic and stearic, also lactic and traces of citric (Leake, 1923) and ascorbic acids (Wright & MacLenathan, 1939), are present on or in the skin, has been proved by much research, of which examples have been given in Section 3.

Since, according to Peck, Rosenfeld, Leifer & Bierman (1939), 0.009% caproic, 0.03% propionic and caprylic, 0.2% lactic, and 0.3% citric and ascorbic acids kill *Trichophyton gypseum*, and since, according to Stock & Francis (1940), the influenza virus is inactivated most strongly by the unsaturated acids with 18 carbon atoms in their chain, it is noteworthy that Hermann & Fürst (1929) claimed cure of fungus infections of the skin by sweat baths, and that the United States Navy Reserve Unit No. 1 (1942) reported inactivation of the influenza virus on the palm of the hand. From all the above evidence there can be no doubt that fatty

acids and soaps, together with other organic acids, are important agents in the antiseptics of the skin.

The fact that the disinfectant power of skin increases with rise of acidity led Marchionini and myself to surmise that H⁺ ion alone is the sterilizing agent on the skin surface. Since many workers, such as Eggerth, Peck and myself, have noted that fatty acids are nearly always more active than their soaps against a variety of bacteria and fungi, and I have observed that hair- and skin-lipoids are more active at pH 4.5 than at pH 7.0, it is likely that H⁺ ion acts not only directly but also by releasing fatty acids from their soaps. Soaps are by no means inactive. Indeed, Lamar (1911) has asserted that soaps are more effective than their acids against the pneumococcus. Herein may lie the explanation of Hermann & Fürst's finding that even alkaline sweat was therapeutically efficient.

The rather disconcerting observations of Usher (1928), Hermann & Fürst, and Cornbleet (1933) that concentrated sweat furnished, even at pH 3.0, an excellent culture-medium for staphylococci and yeasts, whose growth was inhibited on the skin at pH 7.0, may have been due to an unreliable method of recovering bacteria from the skin, namely swabbing. Again, the long-chain fatty acids are probably not present in sweat, they are mainly secreted in the sebum and cling to the skin surface, where they may be sufficiently concentrated to kill even the staphylococcus.

In my experiments on the effect of treating hair- and skin-fats and fatty acids with cysteine, I found that their subsequent ability to kill streptococci was reduced or abolished. In some cases, this ability was restored by subjecting the cysteine-treated extracts to sunlight or ultra-violet radiation, or increased by irradiating the untreated extracts, but, as these substances could not be shown to form peroxides, and as the activity of the saturated stearic acid was more strongly suppressed by cysteine than that of any other acid tested, I cannot conclude that cysteine inhibits solely by reducing peroxides. Moreover, a 1% solution of H₂O₂ was needed to kill one of my test streptococcal strains, and it is inconceivable that such amounts of active oxygen were available in any of the bactericidal extracts or acids used by me. I found also that blood, an oxidizing agent, diminishes the streptococcicidal power of fatty acids, whilst Bayliss has noted the diminution by blood, and Noguchi (1907), Lamar, and Walker the diminution by serum, of the sterilizing properties of soaps. It is probable (Berczeller, 1917, Reid, 1932) that the fatty acids and soaps disinfect by reducing the surface tension of the fluid surrounding bacteria, and du Noüy (1922) has shown how serum, egg albumen, etc. may interfere with this reduction of surface tension. Possibly cysteine causes a similar interference.

Is there any relation between the skin fatty acids and lysozyme? According to Fleming (1922, 1929, 1932) and Wolff (1927a), lysozyme occurs in nearly all body-fluids except sweat, urine and cerebrospinal fluid, but is most concentrated in tears. Of the tissues, cartilage yields the most potent extract in normal saline, skin a weak extract, brain the weakest. Hen's egg-white is the richest source known, being twice as lytic as human tears. Wolff (1927b) tested several common pathogens for sensitivity to lysozyme. *Staph aureus* and *Myco tuberculosis* were as sensitive as *Strept pyogenes*, and *Strept viridans*, *Strept pneumoniae* and *C diphtheriae* were quite insensitive. Lysozyme is inhibited but not destroyed by minute additions of acid and alkali. Its strength is reduced to a quarter by heating at 75° C for 30 minutes, and destroyed by boiling for the same time. It is soluble in water and normal saline, but is precipitated by alcohol, ether, or acetone. It diffuses freely in agar media.

The long-chain fatty acids, on the other hand, are easily recovered from brain-tissue and skin, and it is improbable that there is more than a trace in such substances as tears or cartilage. They are lethal to *Strept viridans*, *Strept pneumoniae* and *C diphtheriae*, as well as to *Strept pyogenes*, and are variable in their effect on *Staph aureus*. Again, a 1/20 saline solution of egg-albumen is harmless to streptococci killed by a very small amount of fatty acids of hair. The fatty acids are as a rule more active in acid than in neutral or alkaline solution. They are stable at 100° C. and are soluble in fat-solvents, but not in water. Streptococcicidal hair-fats, presumably active through their fatty-acid content, diffuse hardly at all through agar media. From these diametrically opposed qualities it is unlikely that lysozyme and

the higher fatty acids are nearly related. Indeed, recent research, such as that of Roberts (1937), of Abraham & Robinson (1937), and of Epstein & Chain (1940), indicates that lysozyme is a protein of low molecular weight with the properties of a polysaccharolytic enzyme. It is questionable whether the sterilizing properties of skin, hair and nails, described by Fleming and attributed by him to lysozyme, were not in fact due to fatty acids and soaps.

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Conclusion

While such factors as desquamation, desiccation, acidity, and sunlight contribute to self-disinfection of the skin, it is probable that the whole range of fatty acids of the acetic series, from formic to stearic and oleic, and to a less degree their soaps, and a few other organic acids are very important agents in killing bacteria, fungi, and viruses on the skin surface.

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MYCOLOGY OF THE SKIN

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It is very probable that the first to suggest that fungi could be responsible for producing skin affections in man were the two brothers Mahon, who visited France in the first part of the nineteenth century to treat "teigne tondante," which was then rampant in the capital. A few years later Schoenlein (1839) and Gruby (1841) independently described the causal fungus of favus, though it was Remak who, a year earlier, noted that the crusted lesion of this affection, the scutulum, differed from that of impetigo in that it contained peculiar threads and spores. During the next decade fungi were proved to be the causal organisms of tinea tonsurans, sycosis parasitaria, pityriasis versicolor, etc.

Problems of Classification

Confusion soon arose in the classification of these fungi, until it was discovered that the cultural characteristics of most of them varied considerably on different media and that, even when grown on the same substances under identical

conditions, they were liable to undergo varying pleomorphic changes. This difficulty was later overcome by Raymond Sabouraud, a pioneer in this relatively new field, whose standard media, the "proof" and "conservation" media, were universally adopted. These media, in their original form, still remain the most satisfactory and widely used for purposes of classification.

The problem of classification has become a very difficult one for, although that propounded by Sabouraud had the great advantage of associating groups with recognized clinical types and was thus appreciated by the dermatologist, it lacked all the criteria required by the botanist. The absence of any sexual forms in the growth of ringworm fungi does not permit any botanical grouping among the Eumycetes and, until such time as developmental characteristics can be produced which would enable them to be placed into any of the recognized classes—the Phycomycetes, Basidiomycetes, or Ascomycetes—they must be relegated to the Fungi imperfecti.

Perhaps the earliest classification was that of Bazin, who was of the opinion that certain fungi had a selective preference for certain tissues, and grouped them under the headings of Epidermophyta, Trichophyta, Onychophyta and Epitheliophyta, according as they affected the epidermis, hair, nails or mucous surfaces. The obvious fallacies and insufficiencies of such a scheme were appreciated by Sabouraud, whose latest classification introduced the Microsporum, Trichophyton endothrix, neo-endothrix (or endo-ectothrix), Trichophyton ectothrix microides, Trichophyton ectothrix megasporae, Epidermophyton and Achiorion. Although most species of the above genera produce similar lesions, this is not always the case, as witness the Achiorion. This genus was introduced to include those species capable of producing the characteristic scutulum but, although *Achiorion gypseum* forms scutula in cattle, in man it gives rise to lesions similar to those due to Trichophyton. Further, although the microscopical cultural characteristics resemble those of Trichophyton, there is a strong morphological resemblance to *Microsporum fulvum*. In an unpublished communication to the Royal College of Physicians about ten years ago the author, in collaboration with P. H. Webb, suggested that a classification of genera depending on the morphology of the macroconidia, could reduce them to three—Microsporum, Trichophyton and Epidermophyton—the species of Achiorion having characteristics enabling them to be placed either among the Microspora or Trichophyta. However, in order to avoid confusion with general usage, the term Achiorion will be retained in this paper for *T. quinckeanum* and *T. schoenleini*.

Plan of Investigation

The dermatologist is expected to be well acquainted with the appearance of the lesions produced by fungus infection, and this may assist him to make tentative suggestions regarding the source of the infection, whether of human or animal origin, and to envisage the course of the disease. He now has the assistance of Wood's light, which readily demonstrates the existence of Microsporum-infected hairs, but he must bear in mind that not all fungus-infected hairs fluoresce as do those of the Microspora. *A. schoenleini*-infected hairs fluoresce poorly and endothrix-infected hairs rarely, if ever, emit any colour. The pathological technique required to carry the investigation further is relatively simple, for potash specimens of either epidermal scales, vesicle caps, hair or nails readily reveal fungal elements, and cultural investigations offer no particular difficulties.

The method of investigating a case of suspected ringworm infection might be conducted along the following lines. First, one should be cognizant of the sites and types of lesions produced; second, infected material should be examined microscopically; third, having confirmed the nature of the infection, material should be inoculated on to a suitable medium. The latter should produce a culture the macroscopical characteristics of which permit identification of the species. Fourth, if there is any doubt about the identity of the growth, a microscopical examination of the culture should help to reveal the genus of the fungus.

The Site and Type of the Lesion

a Groin Discoid lesions, occasionally discrete, but more commonly confluent, often beginning in the inguinal fold and having a tendency to spread more rapidly on the inner aspects of the thighs than the lower abdomen or scrotum and never attacking the hair, usually indicates infection with *Epidermophyton floccosum*. More inflamed lesions may be due to *E. Kaufmann-Wolf* or to *T. purpureum*. The former, though a Trichophyton, is incapable of infecting hair, but the latter may do so as an endothrix.

Moist patches, confined more to the actual fold, are usually due to a monilia and commonly *M. pinoyi*. Copper-coloured, well-demarcated, extensive patches, producing very fine scales, and very slight irritation are characteristic of erythrasma due to *Microsporon minutissimum*.

b Axillae Scaly patches in this region and usually invading, if not actually originating from, the apex, indicate possible infection with *Epidermophyton floccosum*.

c Submammary folds The warmth and moisture, particularly beneath pendulous breasts, encourage the growth of monilia, giving rise to moist, reddish, glazed lesions, but more defined scaly patches are usually due to *E. floccosum*.

d Internatal cleft The lesions and their causal fungi are the same as those found in the mammary folds.

e Feet Scaly patches, usually between the webs of the toes and most commonly between the third and fourth toes are usually produced by *E. floccosum*, but this fungus may also invade the sole and lateral margins of the feet.

Vesicular eruptions on the soles of the feet, occasionally producing large bullae, suggest infection with *T. pedis* (syn. *E. Kaufmann-Wolf*). Sudden, whitish lesions between and beneath all the toes occasionally reveal *M. pinoyi* as the causal organism.

f Hands Ringworm infection of the hands is relatively rare except among farm labourers who may develop raised inflamed discoid lesions, usually beset with numerous pustules (kerion) due to *T. gypseum*, derived from infected cattle.

Circumscribed white sodden patches on the webs and adjacent surfaces of the roots of the fingers, particularly between the third and fourth, have been described under the title of erosio interdigitalis blastomycetica and are frequently due to *M. pinoyi*. The same organism may be responsible for a chronic paronychia, particularly among pastry-cooks and bar-tenders, but bullous paronychia (tourniole) is usually a result of infection with *T. gypseum*.

Symmetrical vesicular eruptions involving the lateral aspects of the fingers and the palms, particularly the thenar and hypothenar eminences are very rarely, if ever, infective, but not infrequently indicate a state of allergy arising as a result of fungus infection elsewhere, e.g. *Tinea pedis*. Such patients are invariably sensitive to mycin (syn. trichophytin), an extract obtained from ringworm fungi.

g Nails Discoloration and thickening, first appearing at the free margin of the nail-plate, which powders more readily on scraping than normal nail, may be due to a Trichophyton or Epidermophyton. It is doubtful whether moniliae, when found in nail scrapings, are causal organisms for they are usually found in conjunction with other pathogenic fungi or in non-infected dystrophic nails.

h Trunk Very superficial, non-inflammatory, patches of a café-au-lait colour are suggestive of tinea versicolor due to *Microsporon furfur*.

Slightly inflamed ringed lesions in children are usually due to *M. audouinii* and rings beset with small vesicles, and concentric rings, are characteristic of *M. felineum* infection.

The Endothrices, particularly in adults, are capable of producing inflamed, broad rings in the centre of which there are scattered follicular papules or minute papulo-pustules.

Discoid, erythematous patches covered with papulo-pustules are pathognomonic of *T. ectothrix gypseum*.

Yellow cup-shaped crusts are the characteristic lesions of favus due to the Achiorion but their fungi may also produce slightly inflamed scaly rings.

i Scalp Scaly discoid lesions, with no appreciable erythema, in which the hairs are broken, having short lustreless greyish stumps (3–6 mm long) indicate Microsporum infection. Microspora of animal origin, e.g. *M. felineum*, produce visible inflammation and the patches are usually more numerous. In recent years a new species, *M. domesticum* (Webb) has been isolated at St. John's Hospital, London, and found to be communicable from cat to man. *A. schoenleini* produces a more diffuse infection in which the involved hairs may retain their normal length, and in some cases the inflammation may be severe and result in atrophic patches. At times the fungus may produce yellowish musty-smelling scutula which eventually have atrophic, single or confluent, pea-sized lesions.

Small bald patches in which the broken hairs do not project above the surface of the skin, and which are sometimes scattered among normal hairs (black-dot ringworm) are produced by Trichophyton endothrix. Inflamed and raised patches (kerion) in which the broken hairs are seen emerging from minute pustules and are readily extracted, are almost invariably due to Trichophyton ectothrix gypseum.

j Beard Circular patches with scaly margins in which the hairs are broken short are commonly due to T. endothrix, but the T. ectothrix usually produce keria.

Technique for Examining Infected Material

The simplest and most efficacious preparation for examining scales and hairs is 7% caustic potash, but 20% potash may be employed for thick specimens, such as vesicle caps and nails, which should be soaked for $\frac{1}{2}$ hour or longer.

TABLE FOR IDENTIFICATION OF COMMON FUNGUS-INFECTIONS

Species	Type of lesion	Wood's light	Microscopical findings	Appearance of culture	Microconidia	Macroconidia	Spiral hyphae	Nodular organs	Chlamydo-spores
<i>M. audouinii</i>	Scalp—scaly circinate patches with short lustreless hair-stumps Skin—slightly inflamed scaly rings	Positive	Hairs—spores arranged as a mosaic around the hair with underlying mycelium Scales—mycelial elements chiefly	Flat, with 3 to 5 radial furrows. Slightly raised central umbo and narrow marginal fringe. Growth visible in 3 to 4 days. Characteristic appearances between 7 to 10 days	Few Elongated	Few Spindle-shaped	None in young cultures	Few	None in young cultures
<i>M. felineum</i>	Hairs—same as <i>M. audouinii</i> but skin more inflamed and tendency to form concentric rings	Positive	Hairs and scales—same as <i>M. audouinii</i>	Flat, with numerous shallow radial folds. Chamols yellow, with lighter centre and central umbo with feathery margin. Slightly quicker growing than <i>M. audouinii</i>	Few Elongated	Abundant Spindle-shaped	Rare in young cultures	Few	None in young cultures
<i>M. domesticum</i>	As <i>M. audouinii</i>	Positive	As <i>M. audouinii</i>	Purplish brown with slightly glabrous (subde) centre and lighter wide margin of fine radiations. Slightly slower growing than <i>M. audouinii</i>	Few Elongated	Few Spindle-shaped and rough-walled	Rare in young cultures	Numerous	None in young cultures
<i>T. crateriforme</i>	Scalp—scaly, with scattered hair-stumps, occasionally minute (Black-dot ringworm) Skin—slightly inflamed scaly patches	Dull blue	Hairs—chains of spores and mycelium arranged longitudinally within the shaft of the hair Scales—mycelial elements chiefly	Small, button-like, white colony with central umbo developing, by the 10th day, a crater with a regular rounded wall. Colour changing to cream or buff	Few Ovoid or spherical	Rare Cylindrical	None	None	Abundant
<i>T. acuminatum</i>	As <i>T. crateriforme</i>	Dull blue	As <i>T. crateriforme</i>	Commencing as <i>T. crateriforme</i> and later becoming more convex, retaining central umbo and developing concentric folds. Cream or buff-coloured	Few Ovoid or spherical	Rare Cylindrical	None	None	Abundant
<i>T. sulphureum</i>	As <i>T. crateriforme</i>	Dull blue	As <i>T. crateriforme</i>	Slightly raised, powdery colonies of a pale yellow or primrose colour and with two or three radial folds. Centre sometimes reddish	Few Ovoid or spherical	Rare Cylindrical	None	None	Abundant
<i>T. cerebriforme</i>	Commonly produces inflamed lesions on the beard and raised ringed lesions on the skin	Dull blue	As <i>T. crateriforme</i>	Begins as white, slightly crateriform colony which rapidly becomes cerebriform and assumes a greyish-white colour	Few Ovoid or spherical	Rare Cylindrical	None	None	Abundant
<i>T. violaceum</i>	As <i>T. cerebriforme</i>	Dull blue	As <i>T. crateriforme</i>	Raised, glabrous, verrucose colony developing a deep violet or brownish violet colour. Slow growing	None or very few	None	None	None	Abundant
<i>T. glabrum</i>				<i>T. glabrum</i> is a fawn-coloured saltant of <i>T. violaceum</i>					
<i>T. gypsum</i>	Scalp or beard—kerions Skin—inflamed, raised and frequently vesicular patches	Negative	Hairs—mycelium and chains of spores arranged longitudinally around the hair	Flat, powdery (plaster-of-Paris) colony. Colour darkening with age from white to café-au-lait. Varieties: <i>T. gyp. asteroides</i> —star-like margin and <i>T. gyp. granulosum</i> —coarse granular surface	Abundant Round and on compound conidio-phores	Numerous Cylindrical thin-walled	Numerous	Numerous	Few
<i>T. pedis</i> (Syn. Kaufmann-Wolf fungus)	Hairs—not involved Skin—usually produces vesicular eruption on the soles	—	Vesicle cap and contents—large quantities of mycelium with tendency to spore formation	As <i>T. gypsum</i> but less powdery and margin less regular. Also raised fluffy, flat velvety, folded and granular varieties	do	do	Numerous	Numerous	Few
<i>T. purpureum</i> (Syn. <i>T. rubrum</i>)	Hairs—not involved Skin—scaly lesions between 3rd and 4th toes spreading on to the foot. Also groins, axillae and trunk	—	Scales—mycelium with little tendency to spore formation	Flat, powdery colony with deep, radial folds. Deep peach colour, darker in the centre	Few Round and on compound conidio-phores	do	Few	Few	Few
<i>E. floccosum</i> (Syn. <i>E. inguinale</i>)	Hairs—not involved Skin—scaly patches between 3rd and 4th toes. Also circinate patches in groins and axillae	—	Scales—long mycelial filaments and large round spores	Greenish-grey, folded colony with raised centre but flat, advancing margin. Growth visible in 3–6 days and characteristic after 8–14 days	None or very few	Numerous Pyriform	None	None	Abundant
<i>A. schoenleini</i>	Scalp—produces typical scutula and, later, atrophy. Also long lustreless hairs	Greyish blue	Scutulum—composed of dense feltwork of mycelium and spores Hairs—longitudinal cavitation and bubble formation within the hair due to degeneration of mycelium	Very slow growing. Visible first after 7–12 days but characteristic 20–40 days. Irregular, very deep folds with waxy surface	Very few round spores	None	None	None	Abundant
<i>A. quincanum</i>	Scalp—not involved Skin—produces scaly or inflamed rings and rarely scutula	—	Scales—mycelium and spores present Scutula—dense feltwork of mycelium and spores	Snow-white, raised colony with delicate, fluffy surface. Growth visible after 2–4 days and advances rapidly with typical appearance after 6–8 days. Centre of colony soon collapses and folding is not uncommon. Emits an odour like decaying vegetables	Round or ovoid spores	Few Cylindrical	None	Numerous	Present

Appearance of Fungus in Scales and Hairs

i *Scales* The pityrosporon of Malassez usually takes the form of gourd-shaped spores 2–4 μ . Round or oval budding spores, with or without thin branching mycelial filaments are characteristic of *M. pinoyi*, but larger masses of spores and more plentiful branching septate mycelium is suggestive of *M. albicans*. Thick, but short, pieces of mycelium with masses of closely-packed spores are typical of *Microsporum furfur*. Numerous short and usually curved lengths of hyphae and scattered spores are suggestive of Achonion. Branched septate mycelium with few or no spores

are found in *Microsporum*, *Trichophyton* and *Epidermophyton*-infected material, but the last two tend to form arthrospores and the latter, longer and straighter mycelial elements

ii *Hairs* Hairs are always involved after infection of the surrounding skin, the fungus growing down in the superficial layers of the follicle before entering the hair. The mode of growth within the hair varies according to whether the fungus is a *Microsporum*, *Trichophyton* (ectothrix or endothrix). An external mosaic of spores with no tendency to chain formation is characteristic of the *microsporum*

Intra-medullary hyphae breaking up into chains of arthrospores is typical of *T. ectothrix* but in *T. ectothrix* the hyphae are found to break up within but chiefly without the hair where the arthrospores still maintain their linear arrangement.

When *A. schoenleini* invades the hair, the mycelium branches and breaks up into short lengths, usually disposed at right-angles to the shaft of the hair (tarses faviques) and associated with irregularly-shaped air-spaces.

Method of Inoculating Media

For comparative examination of cultures it is advisable to employ Sabouraud's original formula

Proof medium

Maltose (Brut de Chanut)	4 g
Granulated peptone (Chassaing)	1 g
Agar	1.8 g
Water	100 cm ³

The maltose should be added last in order to avoid its hydrolysis by excessive or continued exposure to heat, and the medium should be strained through cotton gauze rather than filter paper.

Repeated sub-culture on this medium may produce a profuse overgrowth of sterile hyphae (pleomorphism), and in order to avoid this Sabouraud introduced his

Proof medium

Peptone	3 g.
Agar	1.8 g
Water	100 cm ³

When inoculating the medium with suspected material, care should be taken to avoid the introduction of extraneous, non-pathogenic organisms, but treatment of tissue with spirit or other disinfecting fluid is, in our opinion and experience, valueless. The pathologist's chief concern in this matter is not with the staphylococci or streptococci, which do not grow sufficiently well on Sabouraud's medium to hinder the growth of the fungus, but with contaminants such as *Penicillium*, *Aspergillus*, *Mucor*, etc. which, unfortunately, resist known antiseptics more than do the ringworm fungi.

The dermatophytes grow best at room temperature (25° C) but slow-growing fungi such as *A. schoenleini* can be encouraged if inoculated at 37° C for a few days. For some reason, so far inexplicable, it is particularly difficult to obtain growths from nail scrapings even when there is an abundance of what appears to be healthy, actively-growing mycelium.

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Microscopical Examination of Cultures

There is no appreciable difference in the structure of the mycelium of the various dermatophytes, and one must rely for their differentiation chiefly on the characteristics of the micro- and macroconidia, and on the abundance, paucity or absence of these and other organs such as spiral, racquet or pectinate hyphae, nodular organs and chlamydospores.

a Microconidia These thin-walled unicellular spores may be spherical, pyriform or clavate, and situated either terminally or laterally on the hyphae. These spores are by no means constant, either in shape or number, for any particular species, but as a rough rule one may say that they are elongated and uncommon in the Microspora, are pyriform or spherical, and are numerous and frequently borne on branched conidiophores in the Trichophyta, and are usually absent in the Epidermophyta.

b Macroconidia These large, multinucleated spores, sometimes referred to as fuseaux or spindles, have characteristics sufficiently constant to enable one to recognize whether the cultures are species of Microspora, Trichophyta or Epidermophyta.

The macroconidia of the Microspora are distinctly spindle-shaped, thick-walled, multinucleated spores, having 5-12 compartments, and are pointed at both ends. Those of the Trichophyta are long and cylindrical and thin-walled, having 4-12 segments, and whereas the proximal end is pointed, the distal extremity is rounded. The macroconidia of the Epidermophyta are much smaller, have only 3 or 4 segments, and are club-shaped with rounded free ends.

c Spiral hyphae These are specially characteristic of *T. gypsum* and are hyphal branches having as many as 15 coils.

d Racquet hyphae These are short mycelial segments which are swollen at their free ends but have no diagnostic significance.

e Pectinate hyphae These are formed by the unilateral development of microconidia and are characteristic of *M. audouinii* and *A. schoenleini*.

f Nodular organs These peculiar organs are produced as a result of an irregular knotting of the mycelium and are found chiefly in *T. gypsum* and *A. quinckeanum*.

g Chlamydospores These are thickened, usually intercalary and rarely terminal arthrospores. They are not peculiar to any genus but appear to increase with the age of the culture.

Space does not permit one to dwell at length on the cultural characteristics of the various species, which have been so well described by Sabouraud (1910) and other workers, but the Table (MacLeod & Muende, 1940) may prove useful as a guide to the enquiring dermatologist and pathologist.

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THE ANATOMY OF CUTANEOUS SENSIBILITY

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In order to present, in an understandable form, the modern conception of the anatomical basis underlying sensibility, it is necessary, in the first instance, to review briefly the historical aspect of the problem. An attempt will then be made to present a picture of the neurohistological organization within the human skin, and to suggest how this may be correlated with what has been established in relation to its sensory functions.

Historical

In general it has been conceded by physiologists, psychologists, and clinicians, as the result of observations in recent years, that four primary modalities of sensation can be aroused from the skin, viz. touch, cold, warmth and pain.¹ Other sensations such as itch, tickle, and the sensation of smoothness, to mention but a few, are considered to be the

¹ [For the sake of clarity, only sensations which can be aroused from the skin itself are considered in this article.]

result of a combination of two or more of the primary modalities impinging simultaneously on the central nervous system. It is also conceded that complex sensations, outside the four primary modalities, are dependent for their interpretation on the particular state of the central nervous system at the time of the analysis.

Functional and Morphological Observations

In 1939 Dallenbach published an excellent review entitled "Pain, history and present status", upon which the first section of this article is based. In this review, Dallenbach touches upon cutaneous sensibility in general, but concentrates mainly upon the sensation of pain, for, as he points out, it is about the recognition of pain as a specific sensation subserved by specific sensory terminals, that controversy has mainly occurred until very recent times.

As is well known, the doctrine of the five senses is ascribed to Aristotle, who, however, did not consider that pain was

related to the fifth sensation of "touch" Aristotle classed pain with pleasure, as being among the passions of the soul. Through the centuries following Aristotle, numerous views were expressed concerning the fifth sense. The majority adopted the view that "touch" is based on a plurality of senses, and in the early days it was held that there are as many separate senses involved in "touch" as there are different tactile qualities. As time went on, however, attempts were made to analyse "touch" more seriously, and Galen thought that, in addition to touch proper, there are separate sensations of heat and cold. Nevertheless the majority of observers, including Galen, still considered that pain was not a specific sensation related to specific terminals in the skin, but rather an affective quality depending upon the central interpretation of touch stimuli.

There the matter stood until much later, in 1794, when Erasmus Darwin made an interesting experimental observation with regard to the specificity of heat-sensibility. He described a patient who had lost the sensation of "touch" in one of his feet, and who could feel neither pin-pricks nor pinches. However, when a red-hot poker was approached to within three inches of the sole of his foot, he asserted that he could feel it quite distinctly, and Darwin concluded that, while as the result of disease in his patient the nerves of touch were paralysed, the nerves of heat had retained their irritability. However, Darwin still regarded pain and pleasure solely as "central effects of sensorial motions". In other words, nerve impulses aroused by "touch" might or might not give rise to pain according to the organization of the sensorium at the time of their elicitation.

It was not until 1840, when Johannes Müller enunciated his theory of the specific energies of nerves, that efforts were made to determine whether the skin is subserved by nerves and endings of different specific types. Müller himself believed that sensory nerves yield a number of different sensations and cited tickle, itch, shudder, pleasure, pain, fatigue, suffocation, warmth, cold, touch and movement as among the primary subdivisions of touch sensibility, but he did not postulate different systems of nerve-fibres for those qualities. On the contrary, he attempted to account for them by differences in their mode of arousal and in the state of the organism at the time of their elicitation, so that, as far as the analysis and classification of the cutaneous senses are concerned, Müller added nothing since the time of Aristotle. However, his theory of specific nerve-energies raised an important question. If a given nerve, however stimulated, always gives rise to a specific response, is it not probable that the skin is supplied by a system of nerves which give rise to specific sensations only when the appropriate nerves are stimulated?

As the result of the experimental work which led Müller to enunciate his laws, Blix (1884) and Goldscheider (1898) were led to make experimental observations in relation to cutaneous sensibility, and independently discovered in the skin separate spots for warmth, cold, touch and pain, which, *however stimulated*, yielded only their own specific quality of sensation, and they discovered no other modalities of cutaneous sensibility which could be aroused by single uncomplicated stimuli. They thus first established, on an experimental psychological basis, the existence of the four primary modalities of cutaneous sensibility. However, a violent controversy arose concerning the position of pain as a sensation with a specific anatomical basis. At first, both Blix and Goldscheider were led to infer from their experiments that pain was a specific sensation subserved by a specific peripheral system of nerve-fibres.

In 1894, however, Goldscheider developed a theory in which he once again reverted to the view that pain is mediated by the nerves of "touch", occurring as the result of a central summation of a large number of touch stimuli. In other words, pain in Goldscheider's opinion arises only as the result of an "intense" stimulation of any cutaneous sense organ, and is not in itself subserved by specific nerve-fibres. Frey (1895), on the other hand, as the result of his experiments, maintained that pain is a specific sensibility and punctate in nature, and it should be noted that Frey was almost unanimously supported by clinicians as the result of their own experience.

For some time psychologists, while accepting with reservations the punctate theory of cutaneous sensibility, did not accept the doctrine that pain is a specific sensibility. Not indeed until 1895, when Frey published his experimental

conclusions in which he correlated warmth with Ruffini endings, cold with Krause's end-bulbs, touch with hair follicles and Meissner's corpuscles, and pain with free nerve-endings, were they persuaded to admit that pain might be subserved by a specific peripheral system of sensory neurones.

Despite Frey's work, however, there remained no conclusive *histological* proof that his correlations were correct, and indeed histologists, whilst conceding that the evidence which he offered provided a reasonable working hypothesis, were unable to confirm his observations without equivocation. Waterston (1923), for one, cast doubt on Frey's correlations when he showed that warmth- and cold-spots mapped out on the skin varied in position at different times.

In 1919 Straus & Uhlmann offered proof that pain sensibility shows the phenomenon of adaptation. This was an important step forward, for up to that time it was generally believed, chiefly on biological grounds, that pain does not show adaptation comparable with that displayed by other sensations. It had been argued that pain could not, and indeed did not, show adaptation, for such an attribute would be biologically opposed to survival. However, there was now evidence that pain did show adaptation, thus, if Frey's theory of cutaneous sensibility was correct, then pain should in the course of its adaptation become progressively weaker and ultimately disappear without undergoing any qualitative change. However, Goldscheider (1920) claimed that, in his experiments on adaptation, pain not only becomes weaker under continuous stimulation, but also undergoes a qualitative change. He asserted that pain, before completely adapting and disappearing, passes into a subpainful sensation of contact or pressure. In 1922 Frey, in an experiment to test Goldscheider's theory of subpainful sensations, used sun-rays concentrated by a lens to elicit pain and thus avoided concomitant pressures which occur when a needle-point inserted into the skin is used as a test-object. In this way he was able to obtain pure pressureless pain which showed the phenomenon of adaptation, and he concluded that Goldscheider's theories were untenable.

In 1926 Goldscheider attempted to refute Frey's conclusions on the ground that the latter had used excessively strong stimuli, and that under such circumstances the subpainful pressures are obscured by the intense pain.

In a series of studies following the work of Goldscheider, Dallenbach (Burns & Dallenbach, 1933, Stone & Dallenbach, 1934, Edes & Dallenbach, 1936) did a number of pain-adaptation experiments which revealed conclusively that the nerves of pain are separate and distinct from the nerves of tactile sense. On the physiological side, Gasser & Erlanger (1929) and Adrian (1932) have corroborated their findings by demonstrating that pain is subserved by specific nerve-fibres, as are touch, warmth and cold.

Such was the position in relation to normal cutaneous sensibility considered from the psychological, physiological and anatomical aspects up to 1939. Skin-sensibility was generally considered to be subserved by specific nerve-fibres bearing specific endings arranged in a punctate form throughout the skin and subserving four primary modalities of sensation—touch, cold, warmth and pain, but there was as yet but little histological evidence in support of these theories, and until this was forthcoming they rested upon insecure foundations.

So far no mention of the work of clinicians in relation to the sensory functions of the skin has been made, for it forms a quite distinct aspect of the problem, and is concerned not so much with the punctate nature of cutaneous sensibility, or the position of pain as a specific sensation subserved by a specific system of nerves and endings (hypotheses which clinicians accepted) but rather with the organization of the cutaneous nerves and endings throughout the skin. The experimental work of Head and those that followed him will next be considered.

Experimental Observations

In 1905 Head, Rivers & Sherren published their classical paper entitled "The afferent nervous system from a new aspect". This publication opened up a new field in the study of the sensory functions of the skin, and their theories dominated neurological thought until 1940. Head believed that advances in knowledge would more readily accrue from an experimental study of cutaneous sensibility than from a purely morphological approach, for up to that time anatomical studies had proved comparatively sterile in the search

for an explanation of clinical observations. He therefore studied sensory disorders and interpreted them in terms of normal function. These researches were at first confined to clinical material, but later (Rivers & Head, 1908) he carried out his now famous experiment in human physiology in which he caused one of his own cutaneous nerves to be sectioned and sutured. He then proceeded to study the resulting changes in sensibility, from the moment of section until the restoration of cutaneous sensibility following regeneration.

In these studies, Head was not concerned with anatomical structure, but merely function, and this led him to generalizations which demanded a complete revision of the accepted theories regarding the structural basis of cutaneous innervation. As is well known, he was led to postulate the existence of two systems of cutaneous sensory nerves and end-organs, which he designated protopathic and epicritic, terms which have now passed into neurological language.

Head's physiological experiments were repeated and coupled with more detailed and exhaustive studies by Trotter & Davies (1909, 1913), but their work did not receive the attention it deserved. Their methods were precise, their observations masterly, and their presentation a model of scientific exposition. They were able to interpret their findings without recourse to the postulation of a double system of cutaneous sensory nerves and end-organs. Indeed, as Walshe (1942) has pointed out, the very fact that they were more cautious in their interpretations, and did not find it necessary to introduce any novel terms into neurological literature, is perhaps the reason why their paper was received with little enthusiasm, and may explain the reason why it failed to dislodge the influence of Head's theories of protopathic and epicritic sensibility. Boring (1916) also carried out an experiment involving cutaneous nerve section on himself, and like Trotter & Davies was able to interpret his findings without recourse to a dual system of cutaneous sensory nerves and end-organs. As the result of his observations, however, Boring was led to infer a multiple innervation of sensory spots by fibres and endings of a similar type to provide an anatomical basis for his own observations. Lewis in 1936, also employing experimental physiological methods, deduced the existence of yet another system of cutaneous nerves of dorsal-root origin but not subserving sensory functions to account for his observations in relation to hyperalgesia. This system of nerves he labelled the "nocifensor system."

As Walshe (1942) has pointed out, it is important to note that the structures, whose existence had been postulated by Head and by Lewis, are peripheral and not central, and thus more readily amenable to anatomical proof or rejection.

In 1940 Woollard initiated work on the anatomical basis of cutaneous sensibility which, after his untimely death, was pursued further by Weddell. As the result of these researches, it has been possible to interpret many of the physiological findings of Head, Trotter & Davies, Boring, and Lewis on an anatomical basis, and to confirm the findings of Frey as to the correlation of specific sensations with nerve-terminals of a specific morphological type, with the result that we now have clearer understanding of the sensory functions of the skin.

The Present Position

i Punctate Sensibility In 1940, Woollard, in combined physiological and histological studies, established the fact that pain is subserved in the skin by specific nerve-terminals. He went further and showed that pressure, warmth, touch, cold and pain are represented in the skin in punctate form, as originally contended by Frey (1897), but that the theory of punctate sensibility must be interpreted from a three-dimensional point of view. That is to say, specific receptors lie at different depths beneath the skin. As the result of Woollard's work it can now be definitely asserted that the punctate nature of cutaneous sensory end-organs is established on a sound anatomical and physiological basis.

With regard to the belief that excessive stimulation of specific neural receptors invariably gives rise to pain, Woollard (1940) also made a number of interesting observations. He found that, in every case where staining was complete, specific sensory endings in the skin were always accompanied by accessory fibres of a morphological type similar to those which give rise to pain elsewhere, and he suggested that they might, by their presence there, signal the advent of

potentially harmful stimuli. It is also clear that their presence may account for the wide range of stimuli that are capable of yielding a sensation of pain, and that this idea is quite compatible with the specific activity of each type of end organ. However, the mode and pattern of innervation of the various end-organs still remained unknown.

In the following year Weddell (1941a), in a series of comparative histological studies, and using the technique of vital methylene-blue staining, in which whole preparations of skin in the dogfish, rabbit, monkey and man could be examined, showed that there is a constant pattern of sensory innervation in the skin. In respect of the variety of end-organs, however, the complexity increases greatly through this comparative series, and is greatest in man.

ii The pattern of cutaneous innervation In the dogfish there is a cutaneous nerve-plexus disposed in two main layers through the thickness of the skin. Single fibres travelling in deeper nerve-trunks, when traced peripherally, are seen to change direction and enter a cutaneous nerve-plexus in which they dichotomize repeatedly as they approach the skin-surface. The terminal ramifications of a single fibre become evenly distributed over a wide area which is approximately circular, the final ramifications of the fibres ending freely beneath and between the cells of the basal layer of the epidermis. Neighbouring fibres undergo a similar dichotomization through the cutaneous nerve-plexus, and the terminal ramifications of any one fibre are always evenly interlocked with those of surrounding fibres. The method of distribution of the terminal ramifications may be compared with the branchings and interlacings of a cultivated vine.

In the skin from the ear of a rabbit, the nerve-fibres of which can be evenly stained throughout with methylene-blue, the pattern is strikingly similar to that in the dogfish. A central nerve-trunk enters the base of the ear and soon gives

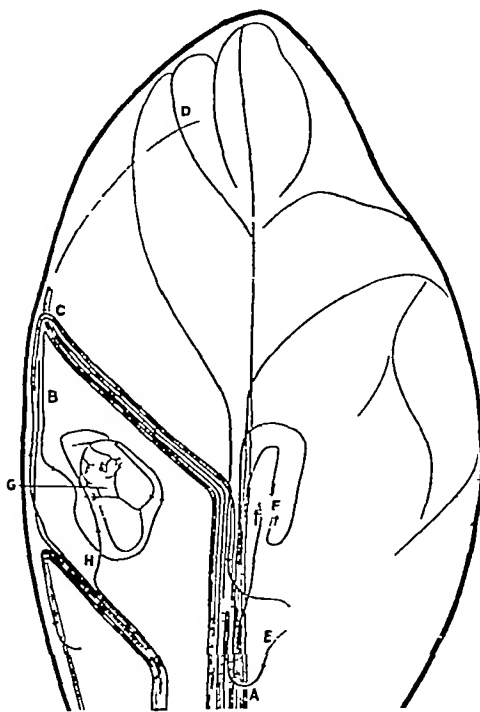


FIG. 1. A line-drawing summarizing the general pattern of the distribution of the nerve-fibres in skin from the dorsum of the rabbit-ear. A, main nerve-trunk. B, marginal trunk. Fibres are passing in both directions. C, nerve fibres innervating. D, intermediate arcade. E, nerve fibre which has run a recurrent course in the main nerve-trunk. F, showing the mode of innervation of a unit area of skin. G, hair follicle group. H, shows the innervation of a hair follicle group by two fibres arising from subsidiary nerve-bundles and passing through the cutaneous nerve-plexus. (Reproduced by kind permission of the editor of the *Journal of Anatomy*.)

rise to large branches which pass up the margins. The central nerve-trunk continues towards the apex of the ear, giving off lateral branches at intervals. These pass towards the margins and divide into ascending and descending trunks which innoscule with other trunks derived in a similar manner. The pattern is complicated at various points by the formation of intermediate arcades and innosculeations which occur between the marginal and central trunks. In the marginal nerve-trunks and the intermediate arcades the nerve-fibres pass in two directions, some passing distally and others returning proximally towards their termination. No nerve-fibres within a nerve-trunk are seen to dichotomize

Fibres occasionally leave one fasciculus to join another in which they may continue distally or return proximally before leaving the main nerve-trunk. In other words, not every fibre in the main nerve-trunk is necessarily passing in a distal direction, on the contrary, some may be running a recurrent course.

It will be observed from this account that there is no question of the nerve-fibres of a main trunk, or of its branches, approaching from one direction, or in approximately parallel formation, the area of skin which they are destined to supply, and then deploying in an even pencil of fibres over the area. On the contrary, to use a botanical simile, the pattern of innervation resembles the reticulate venation seen in certain types of leaves, in contrast to the parallel venation seen in others. Nerve-bundles from the main nerve-trunks give rise to branches which pass up from the subcutaneous layers towards the skin-surface and distribute fibres to the cutaneous nerve-plexus, and the latter is disposed in two main layers through the thickness of the skin. On entering the plexus, the fibres undergo dichotomization. The cutaneous nerve-plexus is formed by the inoculation of the two layers of dichotomized nerve-fibres, arranged in meshwork patterns, which enclose polygonal areas (Fig 2). Hair-follicles lie for the most part at the centre of the superficial polygonal areas enclosed by the nerve-fibre meshwork, and the terminal nerve-fibre ramifications which supply the hairs approach them in several directions from the periphery. In the case of skin from the rabbit's ear, there are two modes of nerve-fibre termination. Some fibres end around the hair-follicles and innervate the hairs, others end in nerve-nets immediately beneath the epidermis. From these nets, fine beaded endings arise which are disposed immediately below and also between the cells of the deeper layers of the epithelium (Fig 3).

Branches of an individual fibre, traced throughout its ramifications in the cutaneous nerve-plexus, bear endings of only one variety. Beneath the epidermis, fibres can be seen arising from nerve-bundles, and in some cases from the deeper layer of the cutaneous nerve-plexus, to form nerve-nets around the larger blood-vessels. The fine fibres leaving the nets to ramify on the walls of the main vessels and the capillary blood-vessels in the subcutaneous areolar tissue at the base of the dorsum of the ear, are accompanied by fine beaded nerve-fibres derived from similar nerve-nets.

After total resection of the dorsal ear-nerve, the fibres supplying the hair-follicles and giving rise to the nerve-nets undergo degenerative changes, and after partial section of the dorsal ear-nerve, the degenerating fibres stand out in contrast to the normal fibres. In one instance it was possible to trace a single degenerating fibre to its termination around the hair-follicles. This fibre was found running through the main and subsidiary nerve-bundles without branching, although it had changed its direction several times. Dichotomization began as soon as the fibre entered the deep layer of the cutaneous plexus. The branches continued to multiply through the plexus and were distributed over a wide, approximately circular, area, the greatest diameter of which was approximately 1 cm. The number of hair-follicle groups supplied by branches from this single fibre was in the neighbourhood of 300, and a group of hair-follicles may contain up to 10 hairs. The terminal ramifications of every main fibre, when traced, were found to remain independent from those of other fibres, but it was noted that each hair-follicle group was supplied by branches from *at least two main nerve-fibres*. This also applies to the individual hairs. The nerve-fibres leaving the superficial plexus usually break up into a number of branches on their way to the hairs, so that a single hair may be innervated by as many as 15 terminal ramifications (see Fig 1).

In skin taken from the thumb-pad of a rhesus monkey, vitally-stained by methylene-blue, a cutaneous nerve-plexus disposed in two main layers was again seen. Its pattern is in general similar to that seen in skin from the rabbit-ear. Arising from the superficial layer are fibres of which each bears one or more endings, but the endings borne by a single fibre arising from the cutaneous nerve-plexus are always of the same type. The following types of endings have been identified—Meissner's corpuscles, Merkel's discs, Krause's end-bulbs, and fibres giving rise to nerve-nets situated beneath the epidermis. Fine terminal fibres arise from the net, and end beneath and between the cells of the deepest layers of the epidermis, and the endings derived from the nerve-nets can be seen to lie in the same optical plane as the epidermal cells.

The nerve-nets from a single fibre are distributed over an approximately circular area, and the nerve fibres from which they arise remain single and unbranched as far as they can be traced through the cutaneous nerve-plexus. The nerve net derived from any one fibre is interlocked with those arising from neighbouring fibres. There is no visible fusion between the interlocked ramifications of nerve-nets derived from separate fibres, on the other hand, there is continuity between the branches of the net derived from a single nerve fibre. The area of skin covered by the net arising from a single nerve-fibre in the thumb of a rhesus monkey is approximately 1.5 mm in diameter.

Observations have been made on human skin stained intravitaly by methylene-blue and removed from volunteers and patients with nerve-injuries. In one instance, a cold spot was mapped on the skin of the forearm and marked by indian ink, by the method described by Woollard (1935). A full thickness of skin, 0.5×0.5 cm, which included the cold spot, was removed. Histological examination showed a cutaneous nerve-plexus resembling that seen in the monkey. Close beneath the surface ink-mark, two groups of Krause's end-bulbs were seen to be borne upon terminal ramifications of thick nerve-fibres arising from the superficial layer of the cutaneous plexus, and situated approximately 1 mm below the skin-surface (Fig 4). The two groups of endings were 0.3 cm apart. They were borne upon fibres which remained separate after being traced for some distance through the superficial layers of the cutaneous nerve-plexus. Meissner's corpuscles, hair-sheath endings, nerve-fibres passing to blood-vessels, and nerve-fibres giving rise to more superficially placed nerve-nets, were seen to be derived from nerve-fibres which ran an independent course within the cutaneous plexus.

In order to investigate the neurohistology of skin from which only one modality of sensation could be aroused, the pattern of sensory loss was outlined in a patient with a sciatic-nerve lesion. The area from which the pain could not be aroused was smaller than that from which touch could not be aroused, and this in turn was smaller than the areas over which temperature had been lost. A piece of skin 2×3 cm was stained and removed from the zone containing (a) the area where the sensation of pain only could be aroused, and also from (b) the area where both touch and pain could be evoked. In area (a) fine nerve-fibres were seen giving rise to superficial nerve-nets, but no thick nerve-fibres or organized endings were seen (Fig 5). On the other hand, in area (b), the cutaneous nerve-plexus was seen as well as thick nerve-fibres ending around hairs, and thinner fibres giving rise to superficial nerve-nets.

In another case, skin was examined from a patient who had sustained a partial interruption of the ulnar nerve. The patient stated that he could not feel the test-object so clearly or strongly throughout the affected area as compared with the corresponding area on the opposite hand, and it was found that two-point discrimination had been virtually lost in the affected area. The skin was stained intravitaly with methylene-blue and removed from the centre of the affected area on the dorsum of the hand. This piece of skin was 3×3 cm, and in one limited field a single stained normal nerve-fibre was seen among degenerated fibres of the cutaneous nerve-plexus. After leaving the plexus this fibre was traced to its terminal ramifications in a nerve-net situated immediately beneath the epithelium, and covering an approximately circular area of 0.75 cm in greatest diameter. There were no interlocking nerve-nets in this area, presumably owing to the degeneration of the immediately adjacent fibres. Arising from the superficial nerve-plexus, and at some distance from the position of the origin of the fibre, giving rise to the nerve-net, were two Meissner's corpuscles borne upon a single thick nerve-fibre (Fig 6).

In summary, it is evident that the pattern of innervation of the skin of a rabbit's ear is such that, in general, each unit-area is evenly innervated by fibres approaching it from all directions. This is brought about by a scattering of the nerve-bundles beneath the skin and the dichotomization of the nerve-fibres as they pass through the cutaneous nerve-plexus, to give rise to endings dispersed over approximately circular areas, and evenly interlocked with endings derived from neighbouring fibres. In the case of hairs, each is innervated by terminals derived from at least two separate nerve-fibres.

There is histological evidence of a similar cutaneous nerve-

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FIG 2



FIG 3

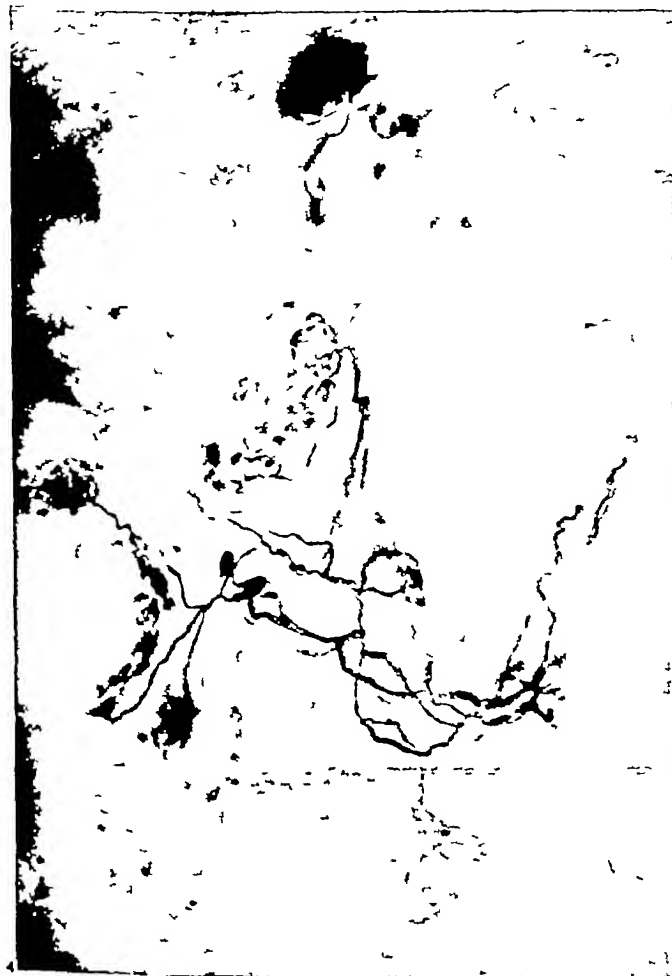


FIG 4

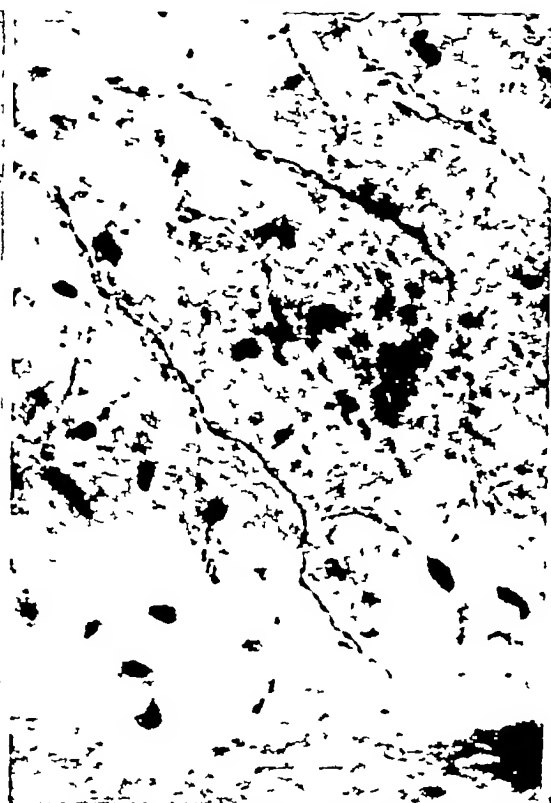


FIG 5

FIG 2. A low-power ($\times 47$) photomicrograph showing the neural topography in the skin from the dorsum of the rabbit-ear. Methylene-blue preparation.

FIG 3. Beaded nerve pain-net arising from fine myelinated fibre in the skin from the dorsum of the rabbit-ear. A cervical sympathetic neurectomy had been performed previously. $\times 520$. (Reproduced by kind permission of the editor of the *Journal of Anatomy*.)

FIG 4. A group of Krause's end-bulbs subserving cold-sensitivity. Methylene-blue preparation of skin from a human forearm. $\times 520$.

FIG 5. Beaded nerve-nets subserving pain. Methylene-blue preparation of skin from the dorsum of a human foot. $\times 400$.

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FIG 6 Two Meissner's corpuscles arising from a single nerve-fibre. Methylene-blue preparation of skin from the dorsum of a human hand. $\times 1,000$

FIG 7 A Meissner's corpuscle from the pad of the fourth finger of a human subject, showing the complex branching and leaf-like expansions of its neural element. Methylene-blue preparation $\times 1,600$. A, Meissner's corpuscle. B, Neighbouring unmyelinated nerve-fibre. C, coiled duct of a sweat-gland. (Reproduced by kind permission of the editor of the *Journal of Anatomy*)

FIG 8 Shows the author's conception of cutaneous innervation based on the studies described in this article. A, groups of Meissner's corpuscles subserving the sensation of touch. B, shows beaded nerve nets subserving pain (probably fast pain). C shows Merkel's discs subserving touch. D, shows beaded nerve-fibres derived from nerve-nets subserving pain and associated with blood vessels (probably slow pain). E, shows nerve terminals around the sheath of a hair subserving touch. F shows a pacinian corpuscle subserving pressure. G shows a group of Ruffini endings subserving warmth. H and I shows groups of Krause's end bulbs subserving cold (these lie at somewhat variable depths beneath the skin-surface). Note—The organized endings are accompanied in every instance by fine-beaded nerve-fibres subserving pain.

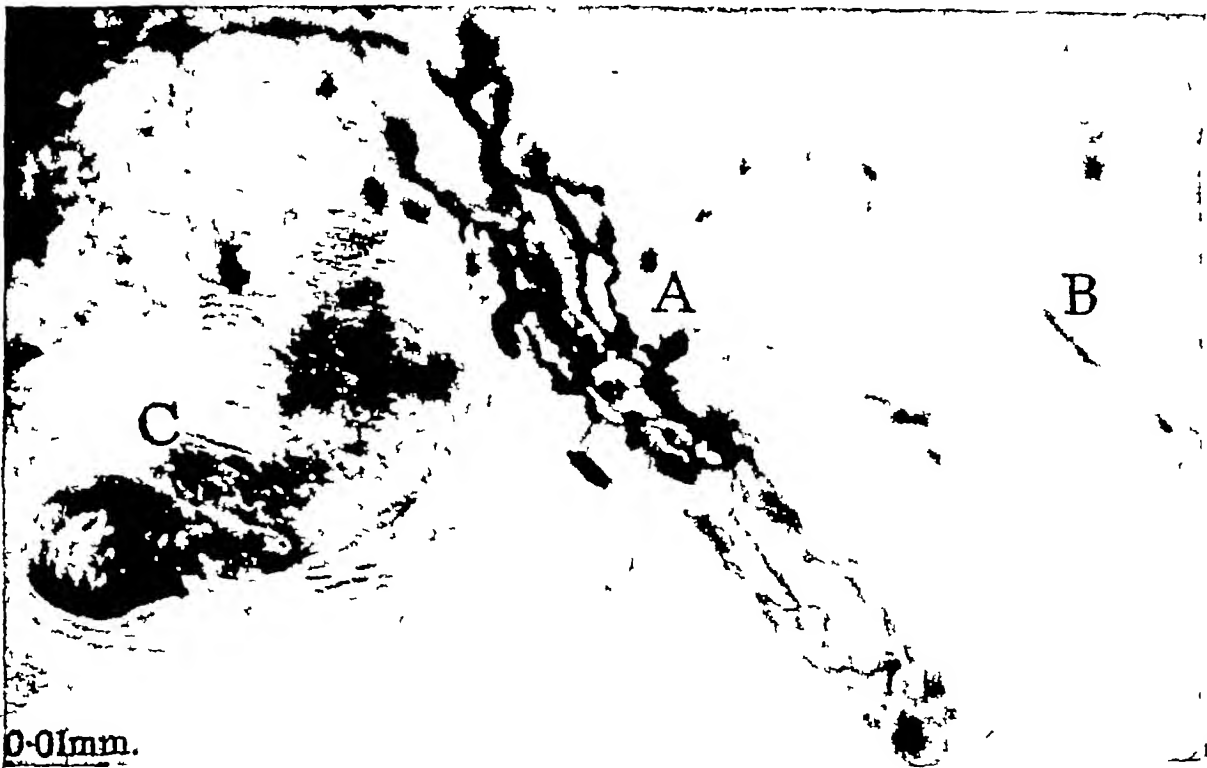


FIG 6

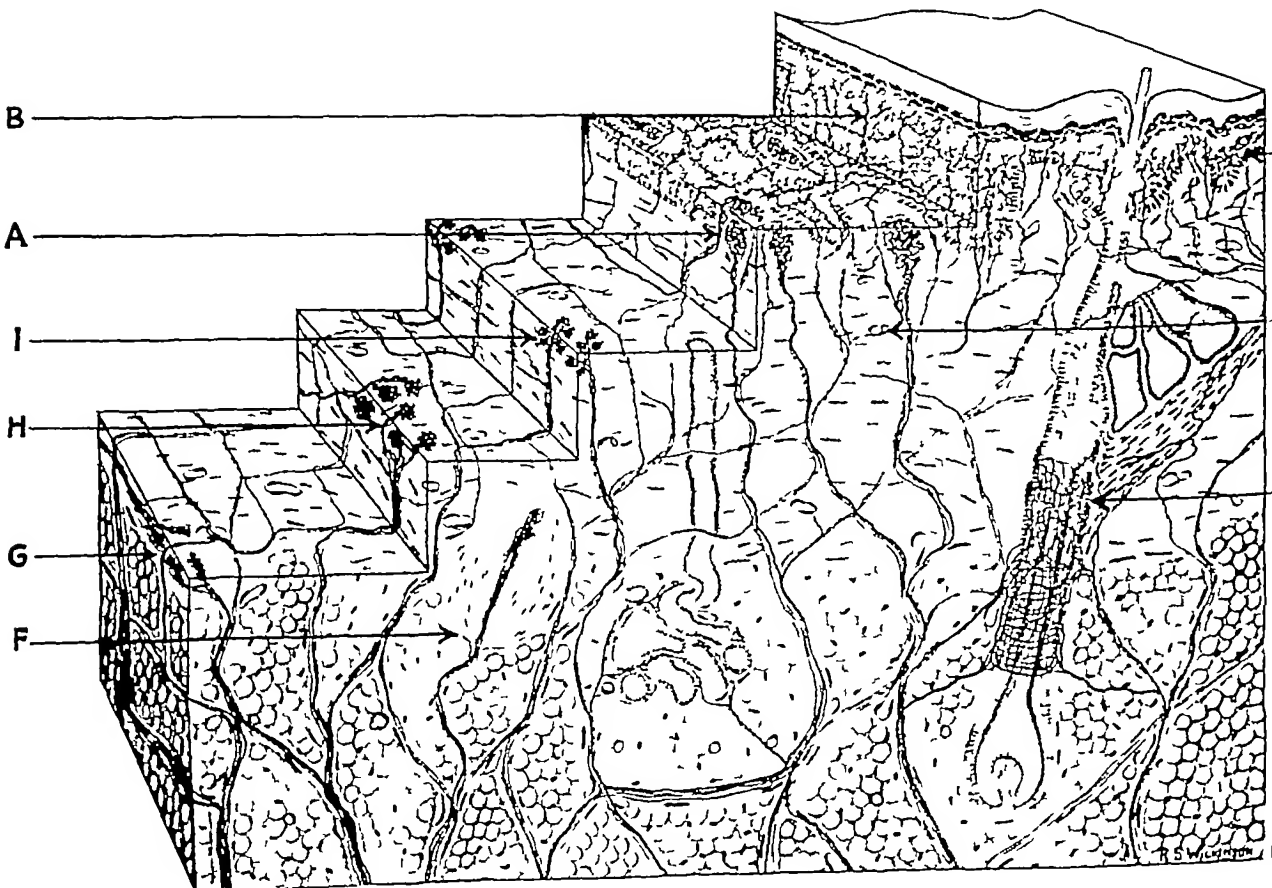


FIG 8

plexus in man, and it has also been established that in areas of skin in which pain alone can be aroused, only fine nerve-fibres giving rise to superficial nerve-nets can be found. It is also of interest that the size of the superficial nerve-nets varies in different parts of the body. On the back of the hand in man a net derived from a single fibre covers an approximately circular area which is 0.75 cm in greatest diameter. This distance is approximately the same as the limen of two-point discrimination of pain in this region. The diameter of the nerve-net derived from a single fibre in the skin of the thumb-pad of the monkey is only 1.5 mm in diameter. This approximates to, but is rather less than, the limen of two-point discrimination in this region in man.

Histologically it is found that, in an area of skin supplied by a partially-interrupted nerve, and in intermediate zones in overlap areas, there are isolated endings, such as single nerve-nets and single Meissner's corpuscles, in contrast to the multitude of endings and close interlocking normally present. From this it is surmised that the powers of localization and discrimination may be dependent at least to some extent on the number of nerve-fibres supplying unit-areas.

iii *Multiple innervation of cutaneous sensory "spots"*
The notion that a single sensory spot in the skin is innervated by more than one nerve-fibre is not new, but until 1941 it had been based entirely on theoretical considerations. It has already been seen from the foregoing description that in the skin of the rabbit's ear, hairs are multiply innervated, and in man this is also the case. In one instance, also, in man, a single cold-spot was found to overlie two groups of Krause's end bulbs.

As regards other types of cutaneous receptor, Weddell (1941b), showed that Meissner's tactile corpuscles are disposed in groups in the skin of human finger-pads. He demonstrated that in an area of acute tactile sensibility in the human skin, each spot is commonly innervated by two or three nerve-fibres approaching from different directions, and ending in separate Meissner's corpuscles (Fig. 7). Such an anatomical arrangement no doubt accounts for the great tactile acuity possessed by the fingers, for it clearly provides for a spatial summation which allows for the recognition of graded stimuli. It would also seem reasonable to suppose that such an anatomical arrangement may be the basis for a tactile localization, for accurate tactile localization implies the recognition of a spatial relationship in the skin, and it may be argued that such a relationship can be subserved only by at least two impulses transmitted by separate fibres from the cutaneous area stimulated.

In the course of regeneration of nerve-fibres in the skin of the rabbit's ear, nerve-fibres were seen (Weddell, 1942) to arrive at hair-follicles at different times, because they approach from different directions and the ultimate courses followed by individual fibres are necessarily of different lengths. Thus, in the course of regeneration there is a phase in which each hair is innervated by a single fibre instead of multiple fibres, and it is reasonable to suppose that the same thing obtains for the various endings in man. Indeed, in biopsy material, such a stage in the course of regeneration has been seen in relation to hair-follicles in man. During this phase there will be no anatomical basis for spatial summation, reactions to stimuli will therefore tend to conform to an "all or none" law, leading to the characteristic explosive type of sensation, and there can be no recognition of gradation, and no possibility of accurate localization.

Boring (1916) suggests that if each sensory spot is projected upon the sensory nervous system as multiple excitations, which depend for their intensity upon their relative strengths, their separation in the region of projection, and a limitation of the available amount of sensory energy, then multiple innervation may be effective either in summation or inhibition of excitations involved. If this is so, then the recovery of only a proportion of the fibres innervating a sensory spot may give rise to the diffuseness and irradiation of sensation which is experienced.

In so-called intermediate zones—those areas of diminished sensibility which are found in zones of overlap between peripheral sensory nerves after section—a reduced number of isolated nerve-endings is found, and it is in these areas that there is an alteration in sensibility which tends to have an irradiating quality, and in which localization is extremely poor, as are also two-point discrimination and the recognition of figure-patterns traced on the skin. In fact, in such areas sensibility is "protopathic" in quality. It will be remem-

bered, however, that the careful experiments of Trotter & Davies showed that in just these areas there is diminished sensibility extending from the normal area and shading imperceptibly into the anaesthetic area.

So far, no mention has been made of the large amount of physiological work on cutaneous sensibility which has been carried out by numerous observers, among whom must be cited Gasser & Erlanger (1929), Adrian, Cattell & Hoagland (1931), Adrian (1931, 1932), Heinbecker & Bishop (1935), Zotterman (1939), and more recently Sarah Tower (1940, 1943), but it is sufficient from the point of view of this article to state, that, in general, the physiological observations which have been made are in accord with the anatomical observations described here.

Finally, in Fig. 8 is shown a conception of cutaneous innervation based upon the studies described above. It thus appears certain that the anatomical basis underlying skin-sensibility consists of specific punctate endings lying at different depths beneath the epidermis and grouped into areas (or interlocked in the case of pain-nets) which can be defined as sensory spots, or to use Tower's (1940) expression, "units of sensory reception."

To permit each sensory spot to be innervated by a number of endings derived from separate nerve-fibres, there is a complex scattering of fibres beneath the skin which is expressed histologically as a cutaneous nerve-plexus. Such an anatomical arrangement accounts for the findings of Trotter & Davies, Boring, and Waterston, and explains many of Head's observations. However, there is no evidence of Head's dual system of sensory nerves and endings, and it now seems probable that "epicritic" sensibility depends essentially upon the multiple innervation of cutaneous sensory spots, a condition which is not present in the case of skin from which "protopathic" sensibility alone can be aroused. It would be interesting to know the details of the pattern of innervation in the skin covering the glans penis, where sensation is normally of the protopathic type, but unfortunately this has not yet been studied.

iv *The Nocifensor System*
In relation to this problem one cannot do better than quote liberally from the excellent review by Tower (1943), in which she states that it is her belief that Lewis (1936, 1942) has unquestionably demonstrated that there is distributed in the skin a system of nerve-fibres deriving from dorsal-roots, having an arborizing pattern of terminal distribution, and not forming a syncytium. This system he has called the "nocifensor" system, considering it to have no afferent function relative to the central nervous system, but to be concerned with the spread of cutaneous hyperalgesia. Anatomists in general have not accepted the concept of the nocifensor system, for there is nothing in their experience to justify it. Woollard, Weddell & Harpman (1940) maintain unequivocally that nocifensor reactions are mediated by the nerve apparatus subserving pain.

Nevertheless, anatomists, and objecting physiologists also, have not faced some of the implications of their rejection, Lewis's argument for separating the nocifensor and pain systems is put briefly as follows. Hyperalgesia may reasonably be conceived to be the ultimate result of a reduction in the threshold of sensory nerves subserving pain, but such a conception should not be allowed to mislead us into believing that pain-nerves form a system through which the local state underlying hyperalgesia is provoked. Lewis believed that the nerves in question could not be those concerned with the conveyance of pain-impressions from the skin, for these, as is indicated by his observations, are accurately located by the subject, and this could hardly be the case if the corresponding impulses enter a system of branching axons connecting to a wide area of skin. The accuracy of this localization he gives as 1 cm or less on the fingers and hand, and it was to preserve a theory of spatial discrimination that he postulated the nocifensor system.

If spatial discrimination could be put on a basis whereby it is not a function of individual neurone units, nor its limen dependent entirely upon their size, then the concept of a nocifensor system would no longer be required.

A striking and general feature of pain-innervation of both skin and cornea permits or very nearly permits, a new theory of spatial discrimination based on analysis of a pattern of activity in overlap neurone units. In 1940 Tower developed such a theory when the extensive overlap of nerves in the cornea was first appreciated. If one can accept the identity

of the pain-sub-serving apparatus and nocifensor system of nerve-fibres, then it follows that maximal areas of hyperalgesia-spread must be related to the size of the largest pain-terminals or units for pain-reception

Up to now there has been no clear demonstration of units as large as 9-12 cm long by 3-4 cm wide (the size of hyperaesthetic zones found by Lewis in the human forearm), and therefore Lewis's own evidence must be accepted as the best yet offered. However, Tower suggests a number of experiments by which the existence of such large terminals could be proved, but she states that until the experiments are done it will only be the bold or foolhardy who think of neurone units of pain-reception of such magnitude

Unsolved Problems

There still remains for solution a number of other problems in relation to the anatomy of cutaneous sensibility, a few of which may be cited

Recent work by Gordon & Whitteridge (1943) leaves no doubt of the accuracy of Lewis's inference that the slow pain and fast pain which can be aroused from the human skin are mediated by separate systems of nerve-fibres. So far, however, two systems of pain-sub-serving fibres and terminals have not been demonstrated histologically. Nevertheless, pain nerve-nets are subserved by fibres, some of which are myelinated and others unmyelinated. Moreover, recent work makes it probable that the pain-nets in the deeper layers of the skin in close proximity to cutaneous blood-vessels are subserved by the unmyelinated fibres, whereas

the more superficially-placed pain nerve-terminals are subserved by the myelinated fibres. The second or slow pain may perhaps be identified as subcutaneous or vascular pain, while the fast cutaneous pain may be related to the more superficial myelinated fibres, but as yet there is no clear proof that this is so

The problem of axon-reflexes remains a mystery from the anatomical point of view. Woollard (1940) was unable to determine the anatomical basis for such reflexes in the skin, but it is true to say that the difficulties of examining large areas of skin in which axon-branching may occur several centimetres distant from the endings, and in which the terminal nerve-nets are so large, is such that an unequivocal statement on the subject cannot be made until further work has been done

Finally, the mechanism underlying the intensification of pain-sensibility which occurs in intermediate zones, and during the course of regeneration after section of a peripheral nerve, and which is so generally referred to by clinicians as pain of "protopathic type", remains a mystery. Recent histological observations by Weddell (unpublished), however, show that there is some correlation between the intensification of pain and the presence of obstructed growth-cones on the terminations of the fibres subserving pain. If these observations are substantiated they will confirm the inference of Trotter & Davies (1909), who believed that the two-phase hyperalgesia following nerve-section was an adventitious affair, considered from the point of view of the organization of the peripheral sensory nervous system

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THE SKIN AND THE RETICULAR TISSUE

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From the days of Kaposi, it has been known that disorders of the blood and blood-forming organs often first revealed themselves by skin manifestations, but a critical integration of dermatology with the pathology of the reticular tissue is as yet in an early stage, although an attempt will be made to review current knowledge of this complex subject

The Reticular Tissue

Aschoff's concept of the reticulo-endothelial system was a logical development from Metchnikoff's description of phagocytosis and recognition of the macrophage, but it is not generally recognized that the reticulo-endothelial system was a physiological system of which the uniting principle was function—the active absorption and in some cases the metabolism of particulate matter, it is now known that the reticulo-endothelial system is concerned not only with phagocytosis and certain stages of metabolism, but is of

paramount importance in tissue immunity and is the site of the formation of antibodies. However, a functional system is distinct from the morphology of the elements concerned, their histogenetic relationship, or developmental potentialities, and it was Alexander Maximow who evolved the theory which forms the groundwork on which the histology and pathology of the reticular tissue is based

In 1898 Marchand had maintained that there were adventitious cells in relation to the capillary wall which were able to form all types of blood and connective-tissue cells. In 1924, Maximow, as a result of detailed experimental work on animals and tissue culture, came to the conclusion that there were scattered throughout the adult body, inconspicuous non-phagocytic connective-tissue cells—undifferentiated mesenchymal cells—which retained the full potentialities of embryonic tissue for differentiating into supporting, phagocytic, or haemic cells. The implications of this idea

for a proper understanding of the pathology of blood-forming organs was not at once grasped, partly because it was confused with an earlier hypothesis of Maximow that the small lymphocyte is an undifferentiated hemic cell, and partly because on the continent of Europe there had been much confusion of thought between a functional and structural concept of the reticulo-endothelial system. In 1932, Dr Beatrice Pullinger, while engaged, at St Bartholomew's Hospital, London, in a study of the histogenesis of lymphadenoma, suggested that "a group of diseases of the reticulum exists in which proliferation is possible into one or several of the possible cell progeny," and that the term reticulosis should be used as a generic title to describe them. In the following year, Dr Joan Ross of the Royal Free Hospital, London, set out a classification of lymph-node disorders in accordance with these views and in 1936 while at St Bartholomew's Hospital, London, I propounded a more complete histological classification on the same lines, which included the leukaemias, the progressive hyperplastic conditions, and the more invasive group or reticulosarcomata (Robb-Smith, 1938). It should be emphasized that the term reticulosis is merely a generic morphological title to describe a group of disorders characterized by a progressive hyperplasia of the cells of the reticular tissue, and is usually restricted to those conditions in which the causation of the hyperplasia is unknown, but in a broad sense reticulosis could include the cellular reactions of this tissue to known infective agents, and the histological changes in typhoid fever or tuberculosis are admirable examples of reactive changes of the reticular tissue.

Histology of the Reticular Tissue in the Skin

Naturally the chief sites of the reticular tissue are the blood-forming organs—the lymphoid tissue, spleen, liver and bone-marrow—but connective tissue is also a part of the reticular tissue, and the dermis is but a specialized form of connective tissue and it is in the dermis that reticular proliferations are observed. The dermis consists of a stroma formed of collagen bundles arranged in different directions and of variable coarseness of fibres, and in amongst these run elastic fibres, there is also a third fibre-form—reticulin—fine fibres which can be demonstrated only by silver-impregnation methods, and are almost certainly of the same histochemical nature as collagen, there is an imperceptible merging from the fine argyrophil reticulin fibril to the non-argyrophil collagen fibre, the difference in the ability to reduce silver completely or partially being probably a physico-chemical one. In addition to running in amongst the collagen bundles, reticulin forms the basement-membrane between the epithelial structures and dermis and the fine stroma lying between muscle-fibres, etc. Although it may be formed by fibroblasts, it can also be formed by other specialized cells which are unable to form collagen direct, and indeed it is probable that it may be formed from ground-substance, as collagen may be, by direct enzymal reaction without cellular proliferation. Running through the dermis are the specialized epithelial structures, muscles nerves and arteries, but in addition, lying around the capillaries and epithelial structure, etc., are undifferentiated mesenchymal cells, and these cells are also to be found between the collagen bundles, in addition there are histiocytes (phagocytic cells)—of which the melanophore is an example—lymphocytes, mast-cells and fibrocytes.

Under suitable stimuli, the reticular cells in the dermis may proliferate and differentiate to form the various mature cells. This occurs as a local process and is not consequent on the transport of cells from elsewhere. Thus, in a healing scar, there will be proliferation of vascular endothelium to form new capillaries, and of fibroblasts to form a new collagenous stroma, if there is foreign material or debris, the histiocytes may proliferate and form giant-cells, in abnormalities of lipid metabolism, the reticular cells are modified to form xanthoma cells, in infections, there will be ingress of neutrophil leucocytes from the bloodstream, but a local proliferation of plasma-cells and fibrocytes, and in tuberculosis and parasitic infections it is probable that some of the specialized histiocytes or epithelioid cells are formed locally. Then there may be differentiation of the mesenchymal cells to form haemic cells, collections of lymphocytes, which may be arranged irregularly or to form follicles, and also of myeloid and monocytoid cells. Further, these differentiated cells need not necessarily be cells normally

found in the body, but may have abnormal characters and show invasive properties.

Pathology of the Reticular Tissue in the Skin

No attempt will be made to review in general the changes of reticular tissue in dermatology, for in every skin disease in which the dermis is involved the cellular changes observed therein are consequent on a reaction on the part of the reticular tissue. On the other hand it is possible to segregate a group of skin disorders in which a reticular proliferation appears to be the principal feature of the disorder, whether in association with a general systematized disorder of the blood-forming organs or apparently restricted to the dermis.

In considering the skin manifestations of this group of disorders, it is necessary to distinguish between the non-specific lesions. Included in the non-specific lesions are the purpuras and spontaneous bruising which are reflections of a haemorrhagic diathesis, which may be associated with severe anaemia, leukaemia a primary capillary defect, or a disorder of the clotting mechanism.

Herpes zoster is another lesion of this type, which is occasionally observed in the leukaemias, but is not infrequent in association with Hodgkin's disease, there is no satisfactory explanation for this phenomenon but it would seem that the virus of the zoster is often to be found in the ganglia of normal persons and is in some way activated by other disease processes.

Pruritus without a specific lesion is also common in Hodgkin's disease, but in the leukaemias it is usually associated with a cellular infiltration and erythrodermia.

In considering the specific manifestations, they will be dealt with in relation to the disease-processes associated therewith, rather than the actual character of the skin lesions produced.

Leukaemias

Skin lesions are most commonly observed in *lymphatic leukaemia* and may consist of a diffuse erythrodermia with a variable degree of scaling or nodular purplish tumours affecting the face, or as small nodules scattered over the body, sometimes the nodules may be limited to the conjunctiva or eyelids. A striking example has recently been described by Stuart (1943). Histologically there is a proliferation of lymphoid cells in the dermis often separated by a line of demarcation from the epidermis. The degree of lymphocytosis bears no relation to the extent of the skin lesions, and although the skin manifestations may be the first symptom there are no proven cases of generalized leukotic involvement of the skin in which the disease was not found to be generalized throughout the internal organs at necropsy. It should be recognized that lymphatic leukaemia is a relatively benign condition, particularly when the total leucocyte count is only slightly raised, patients may remain in good health for 8–12 years after diagnosis as in a case described by Semon (1930).

In *myeloid leukaemia*, skin lesions are much less frequent and usually take the form of purplish nodular tumours limited to the face or widespread over the body, though cases of exfoliative dermatitis associated with a diffuse dermic infiltration of myeloid cells have been observed. Nekám (1937) has provided an excellent review of this subject.

Although *monocytic leukaemia* is the least common form, yet the disease very frequently presents with specific skin lesions, which often precede the characteristic oral lesions and may regress when the disease is fully developed. The lesions may consist of a diffuse eruption of bluish, slightly raised macules or firm pale nodules deeper in the skin. Histologically there is not the intense infiltration seen in lymphoid leukaemia, but the monocytes are congregated round the blood-vessels and sweat-glands or scattered between the collagen bundles.

Hodgkin's Disease

Although symptomatic skin manifestations such as pruritus, non specific pigmentation and herpes zoster are common, yet true involvement of the skin by lymphadenomatous tissue is rare and usually takes the form of plaques on the trunk with a tendency to ulceration. Histologically the epidermis is normal, and there is a narrow zone of dermis above the lymphadenomatous proliferation. In the literature there are many accounts of Hodgkin's disease of the skin but in the

majority of these there is little doubt that a confusion in diagnosis has occurred, and critical surveys such as that of Kierland & Montgomery (1941) from the Mayo Clinic are agreed that skin involvement is a rare complication of Hodgkin's disease

Lymphoid Follicular Reticulosis (Follicular Lymphoblastoma)

This form of lymphadenopathy was first characterized by Brill, Baehr & Rosenthal (1925) and is by no means uncommon. It is a relatively benign condition with a survival period of ten or more years. It occurs between the ages of 40 and 50, usually presenting with generalized lymph-node enlargement sometimes associated with hepato-splenomegaly, the blood-picture is normal, or there may be a slight lymphopenia. The lymph nodes tend to regress spontaneously and are extremely radiosensitive, and there is a striking tendency to serous effusions which may endanger life from cardiac embarrassment. A certain proportion of the cases develop skin lesions which usually take the form of multiple small nodules on the face or trunk, which may regress spontaneously leaving soft depressed scars, occasionally the condition may undergo a sarcomatous change, which is often manifested by the development of large skin tumours which ulcerate and are radio-resistant. The histology is very characteristic, there being large follicles of lymphoblast cells lying in a stroma of small lymphocytes.

Mycosis Fungoides

This curious condition has long been regarded as essentially a skin disease, but recent studies such as those of Berman (1940) have revealed that visceral lesions have been found in almost all the cases examined carefully at necropsy. Baron Alibert named the condition mycosis, as the lesion reminded him of mushrooms, yet this purely descriptive title has confused many people who have regarded it as indicating a fungal aetiology, for which there is no evidence whatsoever.

Striking features of mycosis fungoides are the long prodromal stage, in which the histological changes in the dermis are non-specific, and the characteristic histology of the lesions in the infiltrative stage. In contrast to the skin involvement many reticuloses, in the tumorous lesions of mycosis fungoides the cellular proliferation occurs in the superficial dermis and spreads intra-epithelially. The cytology is characteristic—a proliferation of lymphoblasts, plasma cells, histiocytes and cells which I have described as prohistiocytes and are often multinucleate, there is a minimal increase of reticulum and collagen. Although the cytology has a superficial resemblance to that seen in Hodgkin's disease, yet both the cytology and morphology of the lesions in the skin and internal organs are distinguishable from the changes in Hodgkin's disease, and certainly the natural history of the two conditions is quite distinct. Goldsmith & Payling Wright (1944) have given an admirable account of two completed cases of this condition, though they are not entirely convinced as to its dissimilarity to Hodgkin's disease, on the other hand Cottini (1937), using a critical cytological technique, is of the opinion that the cell type is of the histiocyte series.

Lipidoses

When we consider lipidoses, we turn to a group of conditions, in which, instead of a progressive proliferation of normal or abnormal reticular cells in which the inductive factors are unknown, there is a progressive hyperplasia of reticular cells associated with an excess of lipid within the cells themselves, and therefore it would seem that the aetiology of this condition is easier to comprehend. In reality this is not the case, for if they are described as disorders of lipid metabolism (which they undoubtedly are) we are to a large extent avoiding the question as to what it is that has induced the metabolic disturbances, and it may well be that leukaemia could equally be described as a disorder of nucleic-acid metabolism. In the lipidoses, we do not know whether there is a generalized disturbance of lipid metabolism (possibly consequent on dysfunction of the reticulo-endothelial system) with the imbibition of the abnormal lipids by reticular cells, or whether there is merely a disturbance of intercell metabolism of the reticular cells which is apparent by the retention of lipid within the cytoplasm, and in certain cases by its absorption into the blood-stream. Thannhauser

(1940) has provided a masterly review of this complex problem from all its aspects.

Lipo-melanic Reticulosis (Exfoliative Erythrodermia with Lymphadenopathy)

The group of skin conditions characterized by a generalized exfoliative dermatitis often associated with the names of Brocq, Hebra and Wilson is one of the most confused in dermatology, but of recent years French and American writers have characterized a condition, which is by no means uncommon in Britain, in which males, usually between the 5th and 7th decades, developed a severe exfoliative erythrodermia, sometimes exudative, invariably pruritic, and in which the skin colour ranged from the classical "homme rouge" to a dark brown. In this group there was a generalized lymphadenopathy, sometimes associated with hepato-splenomegaly, and the blood-picture showed a neutrophil leucocytosis with an eosinophilia sometimes of extreme degree, in addition, a certain proportion of the cases showed an abnormal sugar-tolerance curve of the lag type. In the majority of cases they were recalcitrant to treatment, but in some at least temporary improvement has been achieved by dietetic treatment analogous to that suitable for a mild diabetic. The aetiology of the condition is quite unknown, and the histology of the skin is not characteristic—an eczematous change with acanthosis associated with a dermic cellular infiltration of plasma cells, eosinophils and histiocytes, many containing melanin. However, the histology of the lymph nodes is typical and was first described by Pautrier & Woringer (1937) as a lipo-melanic reticulosis, in the peripheral portion of the node there is a cellular proliferation of histiocytes, many of which contain lipid and melanin, and of eosinophils, occurring in the sinuses and juxta-sinusoidal medulla. Although the proliferation is extremely marked, yet I believe it is an exaggeration of a reactive change of a sinus-catarrh type, consequent on the absorption of breakdown products from the abnormal skin. Although the lymph-node change is characteristic of this form of erythrodermia, yet it is not peculiar to it, for it has been observed in the lymph nodes associated with gold-dermatitis and with an exfoliative secondary syphilide.

Boeck's Sarcoid

The individual manifestations of this eponymic disorder have been described by a wide range of specialists from the days of Dr Jonathan Hutchinson of the London Hospital, who first characterized the skin lesions and with a proper sense of values named it after the sufferer, Mortimer, rather than after himself. Yet it is only in the last decade that it has been recognized, chiefly owing to the writings of Pautrier (1940) in France, Longcope (1941) in America and Bodley Scott (1938) in Britain, that the sarcoids of Boeck and Darier-Roussy, lupus pernio, the endothelial tubercle of Ziegler, the uveoparotitis of Heerfordt, the osteitis multiplex of Jüngling, and chronic miliar tuberculosis, were in reality but differing facets of a single polymorphic disorder of considerable chronicity and typical histology.

It is obvious from the nomenclature of the disease, that the early observers regarded the manifestations as having a close affinity with tuberculosis, but in more recent times this view has lost favour, and many would agree with Rich (1944) that it is more likely to be a primary reticular hyperplasia. However, though it is true that there is a little positive evidence that sarcoidosis is a mycobacterial infection, yet there are numerous features that can only lead one to the view that sarcoidosis has close affinities with such an infection. First, the histology of the lesion shows epithelioid systems of the tuberculous type, although there is never any tendency to caseation and seldom any coalescence of the tubercles, culture and animal-inoculation have usually given negative results, but in a very small proportion of cases, particularly where the animals have been allowed to survive for a long period, low-grade tuberculous lesions have sometimes been found from which mycobacteria, slow in growth and low in pathogenicity, have been recovered, this is a line of inquiry which certainly requires further investigation.

Secondly, in the vast majority of cases (indeed some authorities regard it as an essential diagnostic criterion) the Mantoux tuberculin reaction is negative even in a dilution of 1:100, whereas in most countries the majority of the adult population are Mantoux-positive, it is difficult to arrive at a rational explanation for this observation, irrespective of

one's views as to the aetiology of sarcoidosis, though it has been described as indicating a "positive anergy" to the tubercle bacillus. Observations that the serum-globulin is commonly increased have been adduced as evidence of an enhanced immunity to the mycobacteria, but not to the protein fraction on which the skin-sensitivity test is based.

Lastly, a certain proportion of cases of sarcoidosis do develop typical progressive tuberculosis, from which acid-fast bacilli can be recovered, and this is commonly associated with a regression of the sarcoid-type lesion and the development of a positive Mantoux reaction. Thus it can be seen that the mirror-image of a tuberculous infection is often to be observed in sarcoidosis and would suggest that these associations are more than mere chance.

Benign Reticular Skin Tumours

Lymphocytoma cutis is an uncommon condition of which accounts have recently been published by a number of British dermatologists—Klaber (1939) of St. Bartholomew's Hospital, Hallam & Vickers (1939) of the Royal Infirmary, Sheffield and Hellier (1939) of the General Infirmary, Leeds. It occurs most commonly on the face, presenting as milium nodules on the cheeks and forehead, but may be found anywhere on the body or on the mucous membranes. It has a characteristic histological appearance—a spherical collection of lymphocytes with a central area somewhat resembling a Flemming's centre, although eosinophils are often present. It would appear to be entirely benign, with no peripheral blood-change, and is not related to the leukaemias.

The *Spiegler-Fendt sarcoid* is one of those iconograms beloved by the dermatologist which often have little reality as clinical or pathological entities. Spiegler (1894) described a number of cases of elderly persons in which multiple skin nodules of a lymphoid character were observed, and which underwent spontaneous regression and were not associated with blood-changes. Fendt (1900) described a condition in younger subjects which ran a more rapid and fatal course. It would appear to include any dermic lymphoid tumours which are not overtly sarcomatous or leukaemic, and probably includes the skin lesions of lymphoid follicular reticulosis, certain of the dermic reticulosarcomata, and other less well-defined conditions.

The *histiocytoma* has been recognized only of recent years, it occurs as small circumscribed tumours, often sessile and of a yellowish-grey colour. Microscopically they have a superficial resemblance to a fibroma, but have a finer fibre-mesh, and on critical examination are seen to be rich in histiocytes containing lipid and iron-pigment. They appear to be benign. Gross & Wolbach (1943) have suggested that they should be regarded as sclerosing haemangiomas, but the evidence on which this hypothesis is based is not very satisfactory and the view put forward by Alkiewicz &

Suwalski (1939) and others, that they are benign histiocytic neoplasms, appears more satisfactory.

Malignant Reticular Tumours

The differentiation between the progressive hyperplasias of the reticular tissue—the reticuloses and the malignant tumours or reticulosarcomata—is often difficult, for the multicentric proliferation characteristic of the reticuloses is liable to be mistaken for dissemination and invasiveness. The chief criteria on which a histological diagnosis of malignancy of reticular tissue can be based are destruction of the stroma and evidence of metastases of blood- or lymph-borne emboli. The manifestations of the reticulosarcomata in the skin can be divided into two main groups—those in which deposits are incidental features of a disseminated reticulosarcoma, and those in which the tumour is arising primarily in the dermis. In the first group, the masses, which are usually multiple with a tendency to ulceration, may be radiosensitive, but the prognosis is invariably grave, it is not uncommon to find an associated leukaemia, as in the case described by Goldsmith (1933). On the other hand, in those cases in which there is apparently a localized reticulosarcoma of the dermis, although there is histological malignancy, growth is often slow and there is a comparatively good prognosis after complete excision. Should there be a local recurrence, it will respond to radiotherapy, but there is no doubt that surgery combined with radiotherapy is infinitely preferable to radiotherapy alone.

Histologically the reticulosarcomata are very variable, ranging from the poorly differentiated syncytial forms (previously classed as an endothelioma) to the lymphosarcomata.

Kaposi's angiomasarcoma should undoubtedly be regarded as a reticulosarcoma in which there is a proliferation not only of reticular elements but also of vasoformative tissue. It corresponds to the group of reticulo-endothelio-sarcomata, and has certain affinities with *mycosis fungoides*—a slowly progressing prodromal stage which may resemble a hyperplastic process, but with a rapidly increased progression, so that in the later stages its malignant nature can be in no doubt. Post-mortem studies such as those of Choisser & Ramsay (1939) have shown that the interval viscera are usually involved.

In a review such as this, no attempt has been made to discuss the theories as to the pathogenesis of the hyperplasias of the reticular tissue, nor to consider the possible interplay between the reticular tissue and disorders of the connective-tissue ground-substance, such as dermatomyositis or disseminate lupus erythematosus, but there is little doubt that an accurate morphological analysis accompanied by attention to the natural history of the diseases themselves will illuminate an obscure corner of dermatology and may well throw light on the aetiology of such disorders as leukaemia and Hodgkin's disease.

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THERMAL SWEATING

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The body loses heat in three ways—by radiation, convection, and evaporation. Below 88° F. [about 31° C.] (operative temperature) the amount of heat lost by evaporation from the nude and resting man is small, and is not much affected

by temperature (Gagge, 1940), it amounts to about 25% of the total metabolic heat (Newburgh & Johnston 1937, 1942). At higher temperatures the proportion of the metabolic heat lost by evaporation increases rapidly (Fig. 1).

this is shown by the increase in water lost from the skin, thus Kuno (1934) found that, as the air temperature is raised, there is little change in the water-loss from the skin of a resting man until the air temperature reaches about

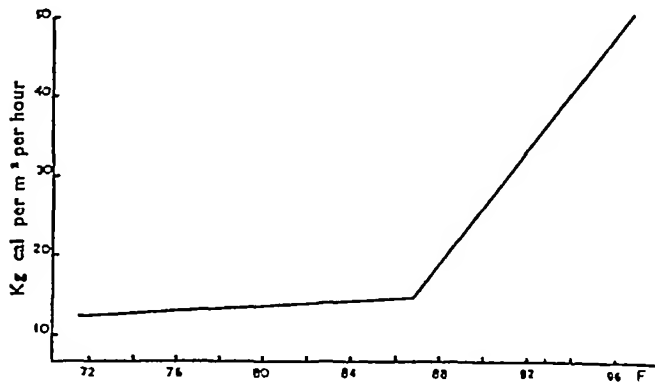


Fig 1
The Increase In evaporative heat loss with Increase In operative temperatures (after Gagge, 1940)

88° F, and then further rises increase the skin water-loss considerably

The evaporative loss below 88° F is the insensible water-loss. Whitehouse, Hancock & Haldane (1932) consider that this water passes through the skin by osmosis, as the rate of loss is diminished by immersion in water, and increased by immersion in strong saline. About 20–30 g of water per hour are lost in this way, also, according to McCance (1936), small quantities of minerals, about 200 mg of sodium and 180 mg of potassium per day (Freyberg & Grant, 1937). Above 88° F the source of the water lost by evaporation is the sweat. There are in man two types of sudoriferous glands, the larger, apocrine, glands have a limited distribution (axillae, pudenda, and round the nipples) and have probably a secondary sexual function, the smaller, eccrine, glands are found in all parts of the body. The thermal sweat is produced chiefly from the eccrine glands. These glands are cholinergic.

The secretion of the eccrine glands is always hypotonic, though at high rates of sweating it may be almost isotonic. The chief constituent is sodium chloride, but it also contains all the plasma crystalloids (Hancock, Whitehouse & Haldane, 1929, McSwiney 1934a, 1934b, Whitehouse 1931, 1935), though they are in most cases more dilute than in the blood. Total and non-protein nitrogen, however, may be twice the blood-level (Talbert, Silvers & Johnson, 1926), the lactate content may also be greater than that of the blood (Mickelsen & Keys, 1943). Potassium is present in some cases in amount equivalent to 11% of the sodium content (McSwiney, 1934b). The pH is variable (Talbert, 1919), according to Whitehouse, sweat is usually alkaline when secreted, becoming acid on contact with the skin. Weiner (1936) found that sweat became less acid as secretion continued.

The chief function of sweat is to provide water for evaporation from the skin, the dissolved constituents in sweat are not of primary importance in this connection, and further consideration of the composition of sweat will therefore be deferred until the rate of sweating and its control have been considered.

Stimulus to Thermal Sweating

Sweating does not start as soon as heat-loss by radiation and convection becomes inadequate. In the unacclimatized subject the rectal temperature may rise considerably before the onset of sweating. Nor is a rise in rectal temperature a necessary stimulus to sweating, the acclimatized subject may start sweating when the rectal temperature is only slightly raised (McArdle, unpublished observations). Even in the unacclimatized, sweating may begin without much rise in rectal temperature, thus Carmichael (unpublished observations) raised the body-temperatures of patients and of normal subjects by placing one or more limbs in water at 113° F, he usually noted visible sweating on the forehead and chest before the rectal temperature reached 99° F, after a rise of about 0.2° F. Kuno (1934) found that subjects semi-immersed in water at 101° F began to sweat on the upper part of the chest after 30 minutes' immersion, when the rectal temperature was rising again after an initial fall.

The influence of skin-temperature was shown by Kuno, he had subjects in air at 113° F with one arm immersed in

water at 40–50° F. This reduced the body-temperature yet sweating continued all over the body exposed to the hot air. Herrington, Winslow & Gagge (1937) believe that radiation initiates vasodilatation and sweating, the radiant energy being absorbed in the skin near the end organs. They find that sweating starts in the nude subject when the skin-temperature reaches 94° F.

Sweating is brought about by the combination of a raised skin-temperature and a rising rectal temperature. Both probably act centrally, as was shown in the experiments by Carmichael already mentioned, in which, when the warmed blood from the immersed limb is prevented from reaching the brain by a tourniquet, sweating does not start until the tourniquet is released, but if the legs of a paraplegic are immersed in hot water, he does not start to sweat until his rectal temperature is very much higher than it is at the onset of sweating in a normal individual.

Rate of Sweating

As environmental conditions become more severe the rate of sweating increases. Eichna, Bean, Ashe & Nelson (1945) have recorded sweat-rates over short periods as high as 3 litres per hour. Equally high sweat-rates have been recorded by McArdle and co-workers, their nude subjects have lost as much as 8 litres in a 4-hour period at 100° F dry bulb, 94° F wet bulb, without working. Clothed working subjects may sweat at this rate at air temperatures 10° F lower. For short periods (30 minutes) the sweat-glands may pour out 60–70 cm³ of sweat per minute. This rapid loss of water from the skin is greater than can be replaced at the time by drinking, Ladell found that, when the sweat-rate approached 50 cm³ per minute, efforts to obtain full replacement of the sweat orally usually led to vomiting, whether water or saline was given.

In general these very high rates of sweating are only seen experimentally. In the Arabian desert Ladell, Waterlow & Hudson (1944) found that men in shorts with moderate activity sweated 500 cm³ per hour in the shade. Dill, Jones, Edwards & Oberg (1933) found daily sweat-losses in the Arizona desert of up to 10 litres. In industry, sweat-rates may be higher, Moss (1922) found that coal-miners may have sweat-losses up to 2.6 litres per hour for short periods, and 8.5 litres for a 5-hour shift. Weiner (1936), working on Bantu in the Rand mines, found sweat-rates almost as high. High sweat-rates are also found in ships' stokeholds and, in the Navy, in shell- and cordite-handling rooms (Critchley, 1945).

High rates of sweating are not maintained for long. Even though all factors are kept the same, the rate of sweating tends to fall off with time (Fig 2). With long exposure this

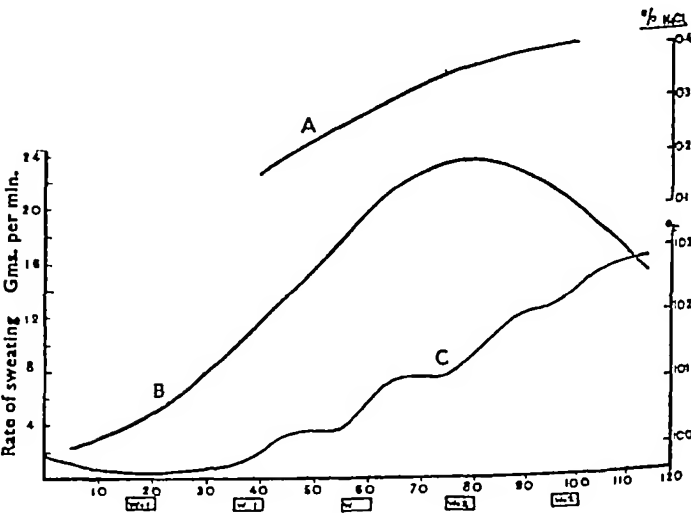


Fig 2
Changes in rate of sweating and in chloride concentration of the sweat during a single exposure at 100° F dry bulb, 94° F wet bulb (Drawn from results of experiment by Ladell)

WX1 WX2 = work periods at different rates
A = chloride concentration (% NaCl) of sweat.
B = Rates of sweating (cm³ per min.)
C = Rectal temperature (° F)

falling off is more pronounced, thus Robinson, Turrell & Gerking (1945) found that the average sweat-rate for six men for the first 2 hours of a 6-hour exposure was 1.31 kg per hour, and for the last hour 0.89 kg per hour. This falling off in sweat-rate with time may be due to fatigue of

the sweat glands (Hancock, Whitehouse & Haldane, 1929) It is not due to dehydration, as it occurs even when all the sweat loss is replaced by water (McArdle, unpublished observations)

Maximum rectal temperature and maximum sweat-rates may not occur together, in one experiment, Ladell found that a nude man with moderate activity at 100° F dry bulb, 94° F wet bulb, sweated 1 560 kg in 30 minutes while his rectal temperature rose from 100 5° F to 102 5° F, and only 1 23 kg in the next 30 minutes when his rectal temperature rose to 103 2° F Rate of rise of rectal temperature is probably as important as the actual height of the temperature Comparison of sweat-rates in hot dry and in hot wet climates shows the effect of skin-temperatures in a hot wet environment the skin is never dry, hence its temperature is nearer the wet bulb, but in a hot dry environment the skin may be quite dry from complete evaporation and its temperature is nearer the dry bulb value, and greater than in a hot wet climate, concomitant with this, it is found that in hot dry conditions, though the heat-stress may be less than in hot wet conditions, the sweat-loss may be greater Thus, McArdle & Ladell (unpublished observations) found the mean sweat loss for 6 men in shorts, working and resting over a 4-hour period, at 96° F dry bulb, 94° F wet bulb, was 2 302 kg, and their final rectal temperature, 100 95° F, the same six men doing the same routine at 120° F dry bulb, 87 5° F wet bulb, and with the same air-movement, sweated an average of 3 327 kg, and their final mean rectal temperature was only 100 6° F

Moderate water-deficiency has no effect on the sweat-rate (Adolph, 1943, Eichna *et al.*, 1945), but in extreme dehydration sweating probably stops Drinking water either to equal the sweat-loss (Pitts, Johnson & Consolazio, 1944) or in excess of it (Ladell, unpublished observation) has no significant effect on the sweat-rate But, if saline is drunk instead of water, the sweat-rate may be decreased (Lee, Murray, Simmonds & Atherton, 1941), especially if the salt-intake exceeds the loss of salt in the sweat, thus Ladell found that the average sweat-loss for 4 clothed men in a 4-hour period under constant conditions was the same whether they were drinking water or 0 1 % or 0 2 % sodium chloride, but reduced 14 % when they were drinking 0 5 % saline The diminution of sweating after drugs of the atropine group may be considerable Scott found that men working in a hot humid environment suffered a 40 % reduction in sweat-rate after taking 2 pills each containing 0 15 mg. hyoscine and 0 4 mg. hyoscyamine

Pathological reduction of sweating occurs in heat-stroke (Manson, 1940) when sweating stops completely, a diminution of sweating also occurs in certain types of heat exhaustion (Ladell, Waterlow & Hudson, 1944, Wolkin, Goodman & Kelley, 1944) In hyperpyrexia the cessation of sweating results in the complete inability of the body to maintain thermal equilibrium, and the rectal temperature goes up to 110° F or more In anidrotic heat exhaustion, there is a raised skin-temperature and a slightly raised blood-temperature.

A man does not sweat at the same rate all over his body Kuno (1934) found most sweating on the forehead, neck and trunk and on the dorsum of the hands, and least sweating on the palm and sole. Burch & Sodeman (1943) measured the rates of water-loss from various parts of the body and found high rates on the fingers, the arms, the axillae and the forehead, elsewhere the sweat-rates were less and all about equal, even though the rates for insensible loss had differed greatly These observers, however, were not working under constant conditions, nor were all their observations taken together Weiner (1945) carried out a detailed survey with these precautions, he measured the sweat-rate over 30 different small areas on the body, and confirmed Kuno's main observations The greatest amount of sweat was from the front of the trunk, there was less on the back, and in general, sweating decreased distally on the limbs, except for the dorsum of the hands which sweated profusely Weiner agrees with Kuno that the different rates of sweating in different parts of the body may be due to variations in the number of sweat-glands By using du Bois' surface-area formulae, Weiner estimated total sweat from the regional rates with an error of loss than 10 % As a generalization, 50 % of the sweat comes from the trunk, 25 % from the legs, and the rest from the head and arms

In a hot wet climate with not much wind, only a small

proportion of the sweat secreted may be evaporated Thus fully-equipped soldiers working at 95° F dry bulb, 85° F wet bulb, evaporated less than 30 % of their sweat when the air movement was low, the clothing absorbed 50 % of its weight in sweat and the rest dripped on to the ground, but when the air movement was increased to 10 m p h, the effective evaporation was increased to 45 % (Ladell, unpublished observations) Thus excess of unevaporated sweat is a safety factor When the amount of sweat produced falls off, e g from fatigue, the subject has still enough sweat to provide the requisite evaporative cooling

Acclimatization

A man newly exposed to hot conditions does not have so good a performance as another man who has been in these conditions for some time Moss (1922) described this phenomenon in coal miners Recently, renewed attention has been paid to acclimatization In the U.S.A., the emphasis has been on cardiovascular adjustment, the greater ability to do work, and the lower rectal temperatures of acclimatized men (Robinson, Turrell, Belding & Horvath, 1943, Bean & Eichna, 1943, Adolph, 1943a, 1943b, Henschel, Taylor & Keys, 1943), and the changes in the blood volume (Bazett, Sunderman, Doupe & Scott, 1940) In England, McArdle (unpublished observations) has studied, in addition, the relationship between rectal temperatures and sweat-rates during acclimatization He finds that, with successive exposures to heat, sweating starts at a lower rectal temperature than before, this change continues for 3-4 days, then, with further exposures, the sweat-rate at a given rectal temperature increases (Fig 3) Weiner, using

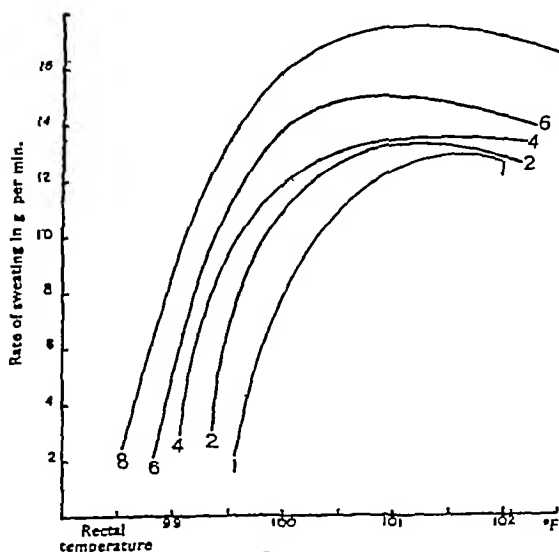


Fig. 3
Changes in sweat rate/rectal-temperature relationship during acclimatization. Numerals indicate the day of acclimatization (after McArdle, 1944)

the technique for determining local sweat-rates (1944) has found similar changes in all regions, but more particularly on the chest. The mechanism of this increased rate of sweating is not known, but there may be, Weiner suggests, a morphological hypertrophy of the sweat-glands McArdle and his co-workers find that sweat-rates may continue to increase, after the first rapid acclimatization, for many weeks, this suggests that the hypertrophy, if it occurs, takes a considerable time to be completed

Factors affecting the composition of sweat

Great variation is found in the mineral content of the sweat. Estimates of the chloride concentrations vary from 0 088 g (sodium chloride) per 100 cm³ (Dill, Jones, Edwards & Oberg, 1933) to isotonic with the plasma (Johnson, Pitts & Consolazio, 1944) There is a great individual variation, for instance, in a series of sweat-samples from normal soldiers in the Arabian Desert (Ladell, Waterlow & Hudson, 1944) the mean was 0 29 % with a range of from less than 0 1 % up to 0 6 %, some patients convalescing after the effects of heat had even higher concentrations up to 0 9 % In general, lower concentrations have been reported from the field than have been observed experimentally

Variations in technique may be responsible for some of the wide differences in the recorded concentrations of chloride

in the sweat. There are three methods possible, the first is for all the sweat produced by the subject to be collected, together with washings from his body, and for the total chloride loss to be measured (used by Whitehouse, Haldane, etc.), a second method is to estimate chloride balance for successive 24-hour periods and apportion the chloride to urine, vomit, etc (used by Keys, etc.) In both these cases the volume of sweat produced is estimated from the body-weight changes and the concentration obtained by calculation, so that only the average concentration over a period is determined. The third method, and the one most commonly used, is to enclose a hand or an arm in an impermeable envelope and to allow the sweat to collect in it. This method has been criticized on the grounds that the chloride concentration of the sweat differs in different parts of the body, Mickelsen & Keys (1943) found 100% difference between arm-sweat and torso-sweat, so that very large errors can result by calculating the total body-loss of chloride from the chloride concentration of hand-sweat and the total sweat-loss. But if a sufficiently large and representative area of the body is used for sampling, this error is obviated. Ladell (1945b) found that the total salt-loss can be estimated with accuracy from the sweat collected from a whole arm, in a series of 16 experiments when the actual salt-losses varied from 2–22 g, the mean actual loss was 5.55 g, and the mean loss calculated from the arm-sweat was 5.67 g, the correlation coefficient was 0.93. This method is therefore admissible.

During a single exposure the chloride concentration of sweat as secreted rises with time (Fig. 2). This rise in concentration is independent of rises in rectal temperature, as it may still continue when the rectal temperature is steady or falling, it may be a fatigue effect (Ladell, 1945a). The same phenomenon has been described by other workers (Johnson, Pitts & Consolazio, 1944, Hancock, Whitehouse & Haldane, 1929, Dill, Hall & Edwards, 1938, Glover, 1931), the relative independence of chloride concentration and rectal temperature has also been noted before (Henschel, Taylor & Keys, 1943). On the other hand, there is evidence that the sweat-chloride increases with skin-temperature (Johnson, Pitts & Consolazio, 1944). The greater the rate of sweating the more concentrated is the sweat, the average salt-loss (4 experiments) of one subject sweating at 10 g per minute was 4.1 g for an initial sweat-loss of 1 kg, when sweating at a rate of 14.6 g. per minute, the average salt-loss (again 4 exposures) for the first kg sweated was 6.3 g (Ladell, 1945a). This has also been reported by other workers but not in the same way, thus Talbert (1919) says "sweat produced while working contains more solids than sweat produced while resting in the heat". An unconfirmed hypothesis in explanation of this is that, when the sweat-rate increases the glands are soon working at their maximum rate of osmotic work, so that any further increases in sweat-rate can be achieved only by reducing the amount of osmotic work necessary for each cm², that is by secreting a less hypotonic sweat.

Talbert & Haugen (1927) reported a correlation between blood- and sweat-chloride, this has been denied by other workers (Mickelsen & Keys, 1943). But in salt-deficiency the chloride concentration of the sweat falls (McCance, 1938), and an increase in the salt-intake, above that required to keep salt-balance, results in a higher salt-content of the sweat (Ladell, Waterlow & Hudson, 1944, Ladell, unpublished). Lee, Murray, Simmonds & Atherton (1941), however, found a drop in the chloride concentration after saline, this may have been due to the reduction in the sweating rate that they found.

The effect of acclimatization on chloride concentration of the sweat is disputed. Dill (1938) and Taylor, Henschel, Mickelsen & Keys (1943) find a drop in sweat-chloride during acclimatization. Johnson, Pitts & Consolazio (1944) consider that any changes there may be are secondary effects due to the lower rectal and skin temperatures of the acclimatized men. McCance (1938) attributes the reported drop in chloride concentration during acclimatization to a minor salt-deficiency, indeed, those workers who have reported an acclimatization effect have kept their subjects on relatively low salt-intakes (Dill, 1938, Adolph & Dill, 1938). In most cases, measurements of the blood-chloride level have not been made, but losses in body-weight are the rule (Adolph 1943a, Ladell, Waterlow & Hudson, 1944). Ladell *et al.* found no seasonal change in sweat-chloride during the

Arabian spring and summer. Serial sweat-samples from men being acclimatized artificially by exposure in a hot room for a few hours each day also showed no changes that could be attributed to acclimatization. But when a subject who had been out of the heat for several months lived in the hot room continuously for 14 days, there were acclimatization changes. During the night, the temperature was just sufficient to promote gentle sweating, but each morning it was raised so that profuse sweating occurred. At first, the chloride concentration rose as this profuse sweating continued, but, after a few days, was no longer seen except after several hours (Fig. 4). With this severe acclimatization the sweat-

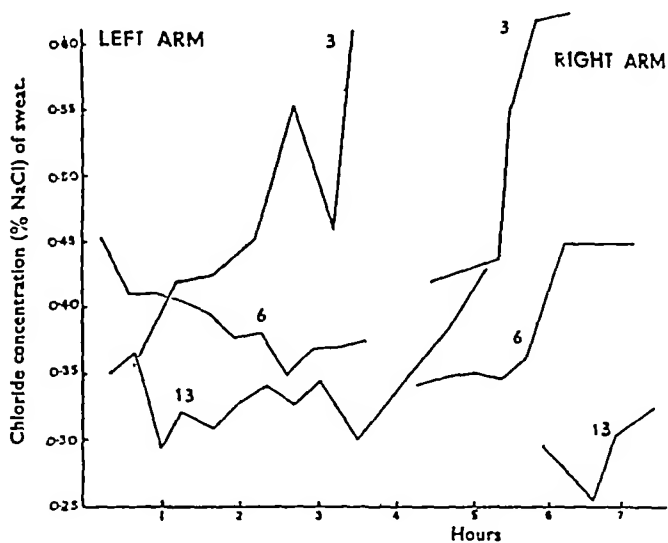


Fig. 4
Changes in chloride concentration of the sweat during a 14-day sojourn in the hot room. Numerals refer to day of experiment. Break between left and right arms coincides with mid-day rest in cooler conditions and shows (day 3) the recovery from fatigue that then occurs. On day 6 the glands showed little fatigue. On day 13 a lower salt-intake was reflected by a lower salt-content of the sweat. (Unpublished experiment by Ladell.)

glands become less susceptible to fatigue. Later, the chloride-intake was reduced by about 10 g per day, so that the daily urinary sodium-chloride output fell from 20 to 10 g, the chloride concentration in the sweat then fell to a lower level, comparable with that found for the same subject when he was living in the desert. A similar drop in chloride concentration was found in four other subjects living in the heat when they reduced their salt-intake (Ladell, 1945a).

The different chloride concentrations of sweat collected in the field, and of sweat collected in hot rooms, may be due, first, to the lower sweat-rates usually found in the field and, second, to this greater resistance to fatigue, a lower salt-intake may also be concerned. A lessening of the tendency for the chloride concentration of the sweat to increase with duration of sweating has been reported by Ladell (1945b) after desoxycorticosterone acetate. Daily administration of 20 mg of this compound gave a reduction of 25% in the sweat-chloride loss. Moreira, Johnson, Forbes & Consolazio, 1945) found suggestive but not unequivocal evidence that adrenal-cortex extract has a similar effect, and that it also reduces the sodium-content and increases the potassium. It is too early, however, to attribute acclimatization to adrenal-cortex stimulation.

When large quantities of sweat are produced, the salt-losses to be made good are considerable, under usual tropical conditions, a total daily intake of 25–30 g is needed (Lancet, 1945), though some workers (Dill, 1938) advise only 10–15 g daily, and claim that no gain is to be obtained by increasing the salt-intake above this level (Taylor, Henschel, Mickelsen & Keys, 1943). If insufficient salt is taken there is danger of heat cramps (Talbot, 1935, Talbot & Mickelsen, 1933), especially if much water is drunk (Moss, 1922, Haldane, 1923). McArdle and his co-workers (1945) find that if a man does not drink he avoids cramp, but when he leaves the heat and begins to drink then cramps develop if he is susceptible to them. The warning, given by Hardt & Still (1941), of "serious physiological consequences" due to loss of vitamins in the sweat is unfounded. Only nicotinic acid is lost in the sweat in significant amounts—0.1 mg per 100 cm³ (Mickelsen & Keys, 1943), thiamin and riboflavin are virtually absent from sweat, and the ascorbic-acid content is negligible.

Ultra-violet rays are absorbed by sweat. Crew & Whittle (1938) found that 75% of the energy of a transmitted beam in the "sunburn" region was absorbed by 1 mm of sweat.

Filtering the sweat reduced its absorptive power, as did extraction with ether, but the clear residual fluid still showed some absorption

Summary

Water loss from the skin is both sensible and insensible. Insensible water-loss occurs when the environmental temperature is below 88° F, and is proportional to the metabolic rate, it is probably an osmotic loss.

Sweating occurs above 88° F in the resting man, or lower if he is working. Thermal sweat is produced by the eccrine glands, which are distributed all over the body.

High sweat rates, up to 3 litres per hour, may be encountered, but such rates are not maintained owing to fatigue of the sweat-glands. The control of sweating is central,

both the skin temperature and the blood temperature are concerned. Maximum sweat-rates are not necessarily found with maximum rectal temperatures, but a high skin-temperature does probably result in a high sweat-rate. Sweat-rate increases with acclimatization.

There is great variation in the chloride concentration of the sweat, both in the same subject and between different subjects. The longer and the faster an individual continues to sweat the greater the chloride concentration of the sweat, but is always hypotonic. Where there is salt-deficiency, the chloride content of the sweat is reduced. Vitamin losses in the sweat are negligible except for nicotinic acid.

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NOTES ON SOME CUTANEOUS MANIFESTATIONS OF DIETARY DEFICIENCIES

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Many nutrients taken in food have now been shown to be essential components of biochemical systems in cells throughout the body—and substantial progress has been made in the elucidation of signs of disturbances of these systems. Parallel with this progress, biochemical and physiological methods have been developed to determine the state of nutrition with respect to various nutrients. Nevertheless, the recognition of signs of nutritional ill-health must continue to be for many purposes, a matter of primary importance. This observation is particularly true of signs in the skin and in other structures readily accessible to the clinician.

Signs in Hair and Skin recorded in Nutrition Surveys

When making surveys of the state of nutrition, I record the following signs in skin and hair. They are given below in the order in which they are recorded in the course of a clinical examination.

Hair of Head

Dry and staring. Hair lacks lustre, is harsh to the touch, staring is the term used to describe a comparable condition in animals (see Fig. 14).

Hypo- or achromotrichia. Diminution or loss of pigment (see Fig. 15).

Skin of Face

Folliculosis Comedo or acne-like lesions (see Fig 13), includes occurrence of *soft* filiform accumulation of sebaceous matter seen especially at the base of the alae nasi

Dyssebacia (Sharkskin) Plugs of dry sebaceous material in follicles of skin of nose, chin and forehead, plug removed makes greasy mark when rubbed on glass slide (Smith, Smith & Callaway, 1941), (see Fig 13)

Skin of Limbs and Body

Atrophic skin Thinning of skin, generally only of legs below knee, skin usually but not always smooth and shiny

Xerosis Xeroderma or asteatosis, dryness of skin, diminution or absence of sebaceous secretion, sometimes also of sweat (see Fig 1)

Crackled skin Ichthyosis-like lesion, more or less scaling—commonest over antero-lateral aspects of calves, mosaic appearance (see Fig 9, 10, 11) Pending further investigation, should be distinguished from crazy-pavement skin (lizard or giraffe skin), (see Fig 5, 8)

"Permanent goose-flesh" Superficially resembles cutis anserina, lesions affect pilo-sebaceous follicles, not frankly keratotic, term introduced because *not* typical follicular keratosis (see Fig 11, 12)

Loss of elasticity Diminution of suppleness of skin seen as fine wrinkling of skin of calves of leg when affected subject is kneeling

Follicular keratosis Firm papules of perifollicular tissue with horny spines of keratin, often with pigmented areola affecting extensor aspects of arms and legs, abdomen, back and buttocks, back of neck and sometimes skin of cheeks (see Fig 1, 2, 3, 14)

Hyperkeratoses Thickening of skin over backs of hands and feet and of skin over joints (callosities), especially knees, elbows, and joints of fingers (see Fig 9, 10), lesion dry and dull, and coarsely wrinkled in appearance, rough to touch

Ulcers and ulcer scars Single or multiple sores confined to skin of legs below knees, occur after injuries such as

and insect bites, scars are thin, shiny and often

increase or decrease of pigmentation in the skin of various parts of the body is also noted

Cutaneous manifestations occurring as frank deficiency diseases (see Fig 4, 5, 6, 7, 16) are generally seen only in patients in hospitals and dispensaries and are recorded separately. It is appreciated that lesions of the skin of the perineum and the skin of the genitalia occur not infrequently in association with other cutaneous manifestations of deficiency disease, but examination of these parts is not usually included in a rapid nutritional survey

Vitamin-A Deficiency

Fig 1 to 3 illustrate the nature of the skin lesion—follicular keratosis (sometimes called phrynodema)—occurring in vitamin-A deficiency. Stannus (1945) gave a summarized description of the condition which he regards as being identical with keratosis pilaris. He suggests that

"keratosis pilaris, as seen among all races, is a reaction in a predisposed skin—to a disturbance in its normal metabolism. The disturbance may be in part traumatic, due to cold, etc., and/or in part nutritional, due to a relative lack of some one or more essential food factors including vitamin A, vitamin E, vitamin B and fatty acids, associated with dietetic deficiency or deficient absorption"

Gross (1944) has recently presented the relationship of this manifestation to keratosis pilaris and to other skin diseases in a more acceptable manner. Folliculosis should not be used as a synonym for follicular keratosis, as by Bourne (1945), who has published a photograph of a skin which is not typical of follicular keratosis due to A-deficiency but rather of keratosis pilaris

The experimental work of Moulton (1943) shows that lesions resembling those seen in man can be produced in rats fed on vitamin-A-deficient diets. Sullivan & Evans (1945) found

"It was possible to delay the signs of vitamin A deficiency by increasing the amount of vitamin B complex in the vitamin A deficient diet and signs of A deficiency were accelerated and intensified by the vitamin B complex deficiencies and deficiencies of fat in the vitamin A deficient diets"

There is evidence from many sources of the association in man of follicular keratosis with signs attributable to

B₂-deficiency (Platt & Gin, 1934, Platt & Lu, 1936). References were made to these observations by Reiss (1936) and Frazier, Hu & Chu (1943), in which Frazier refers to a discussion I had with him in 1935. I cannot agree with the suggestion of Wolbach & Bessey (1942) that

"hyperkeratosis follicularis, frequently reported as occurring among the ill-nourished, especially in the Orient, might be related to riboflavin deficiency rather than A-deficiency, as previously concluded from rather inadequate evidence"

The mode of action of vitamin A on the skin is still unknown, vitamin A is absent from the epidermis (Cornbleet & Popper, 1942)

Dryness of the skin is associated with follicular keratosis and may be regarded in some instances as an early manifestation of vitamin-A deficiency, even when present without follicular keratosis. The dull, slaty appearance of light-skinned subjects and the darkening of the skin of negroes can be attributed to the generalized hyperkeratinization

The hair may be dry and staring (see Fig 14) in subjects with follicular keratosis due to vitamin-A deficiency

Deficiency of the Vitamin-B₂ Complex

The B₂ complex includes nicotinic acid, riboflavin, pyridoxin, pantothenic acid, biotin, *p*-aminobenzoic acid, choline, inositol and "folic acid," crude concentrates of which appear to include xanthopterin, vitamin M and possibly other, as yet unidentified, B-vitamins. Deficiency of all these factors has been associated with changes from the normal of the skin and hair in animals or the plumage in birds. Indeed, the recognition of the existence of some of them has partly depended on the occurrence of these changes. It is also most important to know that some of them are, along with vitamin B₁ and the sulphur-containing amino-acids, intimately concerned in metabolism of the liver

In a comprehensive review, Stannus (1936) groups the signs and symptoms of B₂-complex deficiency under the heading "pellagra and pellagra-like" conditions, he also includes follicular keratosis. More recently he (Stannus, 1944) has attempted "to disengage from the clinical affection we call pellagra, a group of symptoms" which he prefers to call "hypo-ribo-flavinosis" though "uncertainty must still exist as to whether any other factor in the B₂ complex plays a part"

In regard to the manifestations of deficiency of members of the B-complex in the skin and hair of man (including occasional relevant references to cheilosis) the present position may be summarized briefly

Nicotinic acid "The fiery red dermal erythema of all patients blanched after the administration of nicotinic acid, but we did not note any special healing effect on the dermatitis of patients in whom the continuity of the skin had become broken and whose lesions were moist and ulcerated or dry and thickened" (Spies, Bean & Stone, 1938)

Trowell (1941) has described crazy-pavement skin as it occurs in infantile pellagra (or "kwashiorkor"—Williams, 1933). It starts, he writes, as "jet black patches on the skin of the buttocks and the pressure areas of the back and the irritation areas of the perineum. They look as if dull black paint had been painted on to the skin, had dried and had cracked, and was starting to peel off". In addition, "Desquamation occurs early and reveals pale, even dead white, underlying skin. Ulceration easily occurs. Septic lesions are frequent. Fissures occur in the natural folds of the perineum, elbow, axilla, groin and behind the pinna. Generalized pallor of the skin is common. Mosaic skin can also occur. This and this alone is crazy-pavement skin and it is the hallmark of infantile pellagra"

Recently Brown & Trowell (1944), reporting on the "deficiency bowel pattern" in Polish, African and Indian adults as well as in cases of infantile pellagra, state that the dermatoses (crazy-pavement skin) desquamate rapidly when the patient is given nicotinic acid

Riboflavin The recognition that certain skin-changes in man were the result of riboflavin deficiency was due to Sebrell & Butler (1938). They showed that cheilosis and a fine, scaly, slightly greasy desquamation on a mildly erythematous base developed in the nasolabial folds, and later that the condition cleared up on the administration of riboflavin. The photograph in Fig 6 shows changes of the face, eyes and tongue which we now associate with riboflavin deficiency,

CUTANEOUS SIGNS OF MALNUTRITION

Original Illustrations—B S PLATT



FIG. 1



FIG 2

FIG 1 The arm of a young adult Chinese male—upper photograph shows follicular keratosis of flexure aspects of arm—skin dry and wrinkled

Lower photograph—arm of same patient after three months' treatment with a vitamin A concentrate—there are no signs of follicular keratosis—skin is supple

FIG 2 The back of another young adult Chinese male who had been on the same diet as patient with arm shown in Fig 1. Shows follicular keratosis of skin of buttocks and loins—note the length of the keratotic plugs. Skin of arms and back of neck also affected. Recovery was complete after about three months' treatment with vitamin A concentrate

FIG 3 Shows skin from the arm of the same patient as shown in Fig 1 enlarged 2-3 times showing keratinized spiny plugs in skin and prominence of perifollicular tissue

FIG 4 A Russian woman seen in out-patient clinic in a hospital in Shanghai. Shows well-developed case of pellagra of acute type with dermatitis of face and Casal's collar. Extensive lesions of hands and forearms and of lower part of legs. This is the type of skin lesion which heals on treatment with nicotinic acid

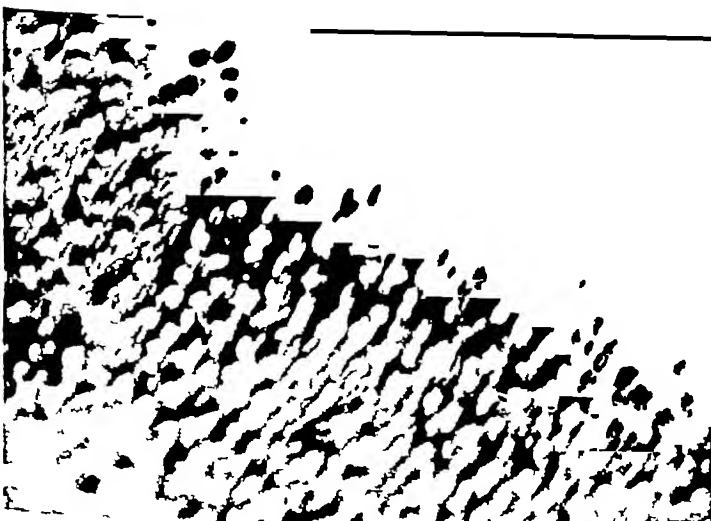


FIG 3



FIG 4

CUTANEOUS SIGNS OF MALNUTRITION

Original Illustrations—B S PLATT



FIG 13



FIG 14

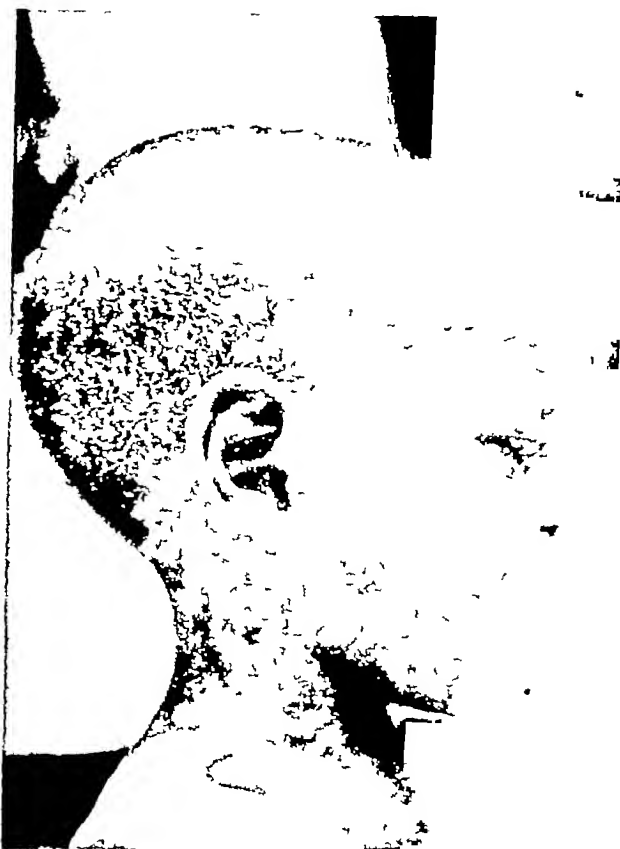


FIG 15

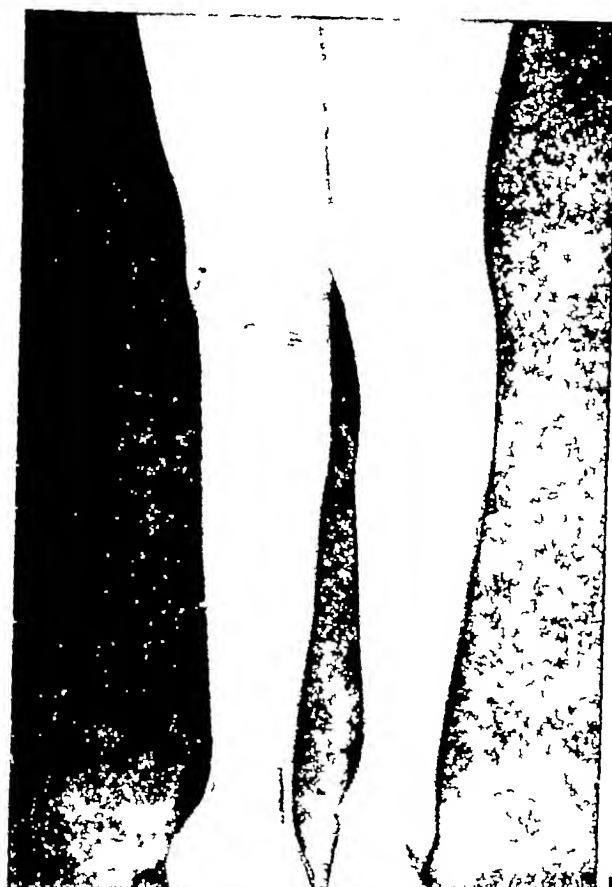


FIG 16

FIG 13 West Indian adult male, an inmate of a lunatic asylum in Antigua, British West Indies. Shows filiform plugs in follicles over skin of nose (dyssebacia), lips and chin. Prominent follicles and folliculosis of skin and cheeks.

FIG 15 An African child of about 4 years of age—a patient of Dr Hughes, Lagos, Nigeria. Hair is straight and shows loss of pigment (achromotrichia). Hair should be jet black and in small, tight curls.

FIG 14 Two Chinese boys, both aged 14 years. The one on the left has dry, staring hair. This was associated with follicular keratosis of skin of cheek in front of the pinnae, also over the skin of the neck and other parts of the body. The boy on the right had been in hospital for some time on a good diet and has well-pigmented glossy hair.

FIG 16 The legs of a Chinese woman showing lesions of acute scurvy: bruise over the right knee and petechial haemorrhages over the skin elsewhere. She bled from the mouth, bladder, rectum and vagina, and required 7 g of ascorbic acid in the course of a week before appreciable amounts were detectable in the urine.

whilst Fig 7 shows the hands of the same patient with lesions of pellagra

Pyridoxin Jolliffe, Rosenblum & Sawhill (1942) have found pyridoxine (vitamin B₆) effective in improving the skin of some patients with persistent post-adolescent acne vulgaris. Independently of the effect on the acne, there was in many of their subjects a marked reduction in the oiliness of the skin, in some cases to the point of causing actual dryness and scaling. Smith & Martin (1940), from their success in the treatment of cheilosis with vitamin B₆, raised the question of the possibility of vitamin B₆ being responsible, at any rate in part, for maintaining the integrity of the lips at the mucocutaneous junction.

Pantothenic acid In the rat, a deficiency of pantothenic acid has been associated with the greying of fur, there does not seem to be any relationship to the greying of hair in the adult (Brandaleone, Main & Steele, 1944). It is quite common to find some loss of pigment (hypochromotrichia) in children who have a deficiency of other members of the B₂ complex. In "kwashiorkor" or infantile pellagra in the African, the hair, instead of being black with small, tight curls is white and straight (see photograph in Fig 15). Dr W. Hughes reports improvement in this condition with the administration of pantothenic acid. The condition is known as "cheveux blancs" in the Belgian Congo.

Field, Green & Wilkenson (1945) report healing of glossitis and cheilosis on treatment with calcium pantothenate after failure to secure healing by administration of other members of the B complex.

Biotin It is now known that "egg-white injury" is due to a substance avidin, this combines with biotin, thereby rendering this factor unavailable and producing biotin deficiency. Sydenstricker, Singal, Briggs, De Vaughn & Isbell (1942) have fed human subjects on a diet containing 30 % of the total calories as egg-white, and produced a fine scaly desquamation of the skin, together with an ashen pallor of the skin and mucous membrane which responded immediately to administration of a concentrate containing biotin.

p-Aminobenzoic acid Sieve (1941) claims that darkening of the hair occurs after administration of *p*-aminobenzoic acid.

Inositol Vorhaus, Gompertz & Feder (1943) reported that two cases of pruritic, scaly eruption responded to treatment with 1 g. of inositol daily.

Concentrates of the B-vitamins

Dyssebacia (using the term as defined above—see Fig. 13) does not respond to treatment with known members of the B₂ complex, but is cured by administration of autoclaved yeast or liver extract (Smith, Smith & Callaway, 1941).

Gross (1941) has had good results on treatment with B₂-rich preparations in several skin conditions, and has recently (Gross, 1944) claimed a curative effect of the cutaneous lesions of psoriasis using soya-bean phosphatides and wheat-germ, which supply choline and inositol.

Field, Farnall & Robinson (1940) describe as features of chronic pellagrous dermatitis, hyperkeratoses (see knee and dorsum of foot in Fig 9) and an ichthyosis-like change, apparently similar to, if not identical with, "crackled skin" (see Figs 9, 10, 11). These sometimes clear completely within 2 to 3 weeks, sometimes only after many weeks, and occasionally they show only partial improvement after long continuation of treatment with the whole vitamin-B complex in comparatively large doses.

Gillman, Gillman, English, Friedlander & Hammar (1944) report failure to cure cases of "malignant infantile pellagra"—with pellagrous skin lesions, grey hair or alopecia, and fatty livers—using vitamin B₂, nicotinic-acid, yeast, or liver extract, but they had dramatic success with a stomach preparation (ventriculin, Parke-Davis) and hydrochloric acid.

Amino-Acids

Attention has been directed recently to the possibility of deficiency of essential amino-acids in the development of ulcers in tropical countries where cutaneous evidences of B₂-deficiency are common (Platt & Webb, 1945).

Experiments of Croft & R. A. Peters (1945) have shown that 1 % methionine in the diet substantially reduces the losses of nitrogen in the urine after skin-burns. Relevance of this observation to the experimental development of skin ulcers is being explored. B. A. Peters (1945) claims to have

improved two severe cases of exfoliative dermatitis by administration of cystine or cysteine, and shows that in one case some 40 % by weight of the protein intake was being lost by the desquamated skin.

Vitamin-C Deficiency

Haemorrhage into the skin is the classical manifestation of scurvy (see Fig 12). Scarborough (1943) has presented evidence that vitamin P is also concerned in lesions of this type. Vitamin-K deficiency may also give rise to similar lesions (Kark & Souter, 1941). Jeghers (1943) has recently reviewed these signs in relation to nutritional factors.

There seems to be little doubt that the earlier observations of scurvy were correct in including a keratosis of the pilosebaceous follicles as a manifestation of vitamin-C deficiency. Scheer & Keil (1934) recognize that this keratosis was associated with involvement of the perifollicular capillaries, it could not always be detected clinically, though it could be elicited as perifollicular petechiae on applying pressure by a tourniquet.

Crandon, Lund & Dill (1940) show quite conclusively that a "follicular keratosis" can be produced in man on a vitamin-C-deficient diet containing adequate amounts of vitamin A.

General Considerations

A proper appreciation of the significance of clinical evidences of deficiency diseases involves consideration of the following factors.

Physical signs of diseases may be encountered, similar in many respects to those associated with dietary deficiencies but not necessarily attributable to faults in the diet, these must be differentiated.

Factors such as environmental stress and infection contribute to the clinical expression of nutritional deficiencies (Platt, 1944).

It may be difficult to determine readily whether a particular sign is due to insufficiency of one of two or more nutrients.

Again, the appearance of the lesion due to a dietary defect varies according to its age or rate of development, or to the degree of the deficiency, or to a combination of the degree and duration of the deficiency.

Diagnosis of the more florid deficiency states is easier than of minor manifestations. One reason is that gross manifestations are often due to deficiency of a single food-factor, whilst the minor manifestations are almost always multiple. Experience with the well-developed signs is a good foundation on which to base a study of the early stages of mixed deficiency disease. The cutaneous signs of nutritional ill-health are elements of syndromes and advantage should be taken of this fact in arriving at a diagnosis. Evidence is accumulating that changes in the skin may be related to, if not indeed determined by, disturbances due to the effects of dietary deficiencies in other tissues and organs as, for example, in the liver and alimentary canal.

Knowledge of the nutritive values of foods has made it possible to arrive at an accurate evaluation of several nutrients in the dietary, information of this kind should be obtained and related to the clinical findings. The prevalence of signs in a community may be correlated with the results of the evaluation of food statistics for the whole community, this type of investigation is a valuable adjunct to the detailed study of individual patients. In the examination of dietary data on certain nutrients, particularly those of the B group, care is needed in interpretation on account of the possible contribution to the amounts absorbed by the body of syntheses by micro-organisms, or, on the other hand, to losses by destruction in the alimentary canal.

Examination of tissues by conventional histopathological methods may be of assistance, but the results may not be more precise than those obtained from clinical examination. Observation of the effects of treatment with single nutrients may be dramatic and, especially in the florid deficiency states, may confirm a diagnosis. There is some evidence that the administration of large doses of single nutrients may upset metabolism in such a way as to lead to signs of deficiencies of other food factors. Long-standing lesions may, however, respond only slowly, or incompletely.

Experiments on animals may contribute to the elucidation of the relationship between diet and disease. Different animals respond in different ways to individual nutrients,

and some animals may not require certain nutrients at all, so that the application of the results of animal experiments to the study of deficiency disease in man must be made with caution

Comment

The text of this paper taken together with the photographs should help in the recognition of some cutaneous manifestations of dietary deficiencies. It will be evident to the reader that there is a problem in deciding on the nomenclature of these signs, and I fully appreciate that complete agreement cannot yet be achieved. Similarly, in the related problem of

the interpretation of these signs in terms of dietary defects and ultimately of the underlying metabolic disturbances, a great deal more investigation is obviously needed. Questions relating to recognition, nomenclature and interpretation arose time after time in a recent medical survey of nutrition in Newfoundland (Adamson *et al.*, 1945). In investigations in the West Indies and West African territories, I have had opportunities to give further consideration to points of difference which will appear if the report of the Newfoundland survey, especially the illustrations, is compared with the present paper. A fuller and more extensive presentation with more illustrations is in the course of preparation as a glossary of signs of nutritional ill-health.

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² [BMB 103]

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SCIENTIFIC PRINCIPLES IN THE DESIGN AND CHOICE OF OINTMENT BASES

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Medicated ointments and their bases are amongst the oldest preparations used by mankind for the treatments of wounds and disorders of the skin. It is truly remarkable that the particular base employed, namely animal fats, vegetable oils and waxes, did not vary much during the ages. They are mentioned in the Book of Exodus, the formulae of the Papyrus Ebers and in the practices of Avicenna and Galen. They included lard and suet, neatsfoot oil [*Oleum bubuli*], beeswax, the so-called bear's grease, hedgehog fat, goosegrease, and oils of almond and olive. With the exception of lard, the animal fats have long been either discarded or relegated to the domestic medicine cupboard. It would be wrong, however, to dismiss these bases as useless, for most of them, particularly goosegrease, do possess the property of rapid absorption by the skin and, when absorbed, of being readily metabolized. This property is a valuable one in dermatological practice. Unfortunately, because they contain glyceryl esters of unsaturated fatty acids, they are liable to develop rancidity, which brings in its train irritation in use and a disagreeable odour to offend the fastidious. Lard has survived because quite early it was discovered that it would dissolve out from Siam benzoin, an antioxidant which would preserve it against rancidity.

To-day we know of other and better antioxidants, such as ethyl or propyl gallate, which will preserve these animal fats and vegetable oils from rancidity without introducing complications in their usage. Thus benzoinated lard is still included in both the British and United States Pharmacopoeias, but modern developments have made it almost obsolete. Neither of these authorities utilizes it now for

any medicated ointments. The last preparation, mercury ointment B.P. 1932 has gone, the lard having been replaced with a more modern base. It is difficult to give a reason other than sentimental for the retention of benzoinated lard as an official preparation, since in spite of its absorptive value it has so many objectionable features. It can be irritating in use, it is liable to react with and inactivate many medicaments, and the patient dislikes it because it is greasy.

Bases of Relatively Recent Introduction

Early in the nineteenth century, paraffin provided entirely new types of bases. Soft paraffin (vaseline) and hard paraffin, in admixture or alone, could provide a wide range of consistency from very soft to very hard. They could be prepared so that they were bland, non-irritating, neutral and non-reactive. Most important of all, they could not go rancid. The paraffin bases differed fundamentally from the older bases in that they were poorly absorbed by the skin and could not be metabolized after absorption. Their action on the skin was therefore limited to surface-effects. Their freedom from irritant effects made them valuable for the medication of delicate tissues such as the eyes and nose.

The appearance of wool fat (a more correct name would be wool wax) in the 1898 British Pharmacopoeia heralded an entirely new type of base, one which was capable of absorbing or emulsifying water or aqueous solutions to give a water-in-oil emulsion. Being of animal origin, it was readily absorbed by the skin and, if purified, did not go rancid. Used by itself, it was generally too sticky, but in an emulsion together

with some fixed oil or paraffin base it was of a creamy consistency and became popular as a base for cosmetic preparations. Wool fat provided many new types of ointment and new lines of treatment in dermatology.

Other types of bases were developed, such as the various glycerin bases, glycerin of starch and glycogelatin. Glycerin of starch B.P. and similar preparations have a special place in dermatology when the presence of grease in treatment is contra indicated, and in quite early experiments such bases proved to be quite readily absorbed, owing probably to the glycerin content. Glycogelatin base has proved useful where prolonged non-greasy contact with the skin is required, as in the case of Unna's paste. It has been used successfully for the application of the sulphonamides and it is probable that it would be successful with penicillin.

Glycerin is a good skin penetrant, and percutaneous medication is attempted by glycerin pastes such as glycerin of belladonna, iodoform and ichthammol, which are probably effective. Percutaneous medication by plasters is now almost obsolete, although belladonna (breast) plaster still retains its place in the Pharmacopoeia. The latter, however, gives permission for the basis to be either of the old resin plaster type or of rubber. Any absorption from the rubber basis is doubtful, for in attempting an assay process it is extremely difficult to extract the alkaloids from a rubber plaster by solvents.

Percutaneous medication by means of preparations having as their base flexible collodion, and thus producing a medicated film on the skin, are extremely suspect (Berry & Goodwin, 1937), for should the film be a good one, retaining and not extruding the medicament, no action occurs. If it extrudes the medicament on drying, there is no reason for the collodion basis, a glycerin paint would be a better substitute.

Finally soap bases as pastes or liniments have been in common use. There is no doubt that soap is readily absorbed by the skin and is capable of carrying medicaments with it. It should be a useful medium for many bactericides, particularly phenols, in skin treatment.

Dermatological Requirements of an Ointment base

Thus, then, was the general picture of the type of dermatological ointments and pastes of some ten or fifteen years ago, but remarkable advances have since been made in the production of a series of new substances and preparations which will undoubtedly be of great value to the dermatologist. For this we have to thank the science or art of cosmetology which, in this era of lipsticks, creams and powders, has initiated research in the production of new substances, particularly cream bases, which offer a wide range of new media for trial in dermatology. Cosmetology can provide elegant preparations ranging from the purely oleaginous to emulsion-creams of both the oil-in-water and water-in-oil types, together with a range of mucilaginous ones in which nearly every physical factor has been studied, such as pH, consistency, absorption and degree of dispersion. The interest of the dermatologist was directed to these new products by Mumford (1938) in a paper on emulsifying bases in dermatology, in which he proposed the use of a base to which medicaments in aqueous solution could be added, thus forming an elegant cream of the oil-in-water type, incorporating an ingredient introduced by cosmetic preparations. This was the beginning of many other suggestions and trials from which we now have some accumulated experience.

Before dealing in detail with these new compounds, however, it is advisable to consider, from the dermatological point of view, the skin as the site of application. Thus skins may be greasy, even excessively greasy as in various conditions of seborrhoea, or greaseless and dehydrated as in eczema. It has been fairly well established that when oils or fats are absorbed by the skin the main route is via the hair-follicles and through the sebaceous glands. The intact epidermis itself is not penetrated to any appreciable extent by these bases.

In general the skin is impervious to most aqueous preparations, although certain medicaments seem to have the facility of penetration and absorption irrespective of the medium in which they occur. Thus methyl salicylate, mercury and the mercurials, salicylic acid and, in particular, boric acid are capable of passing through the living intact skin with considerable freedom. Indeed, boric ointment

almost stands condemned as a poisonous substance. There is, however, a large class of medicaments which do not readily penetrate, and it is in these cases that the choice of the base is important if penetration is desired. In such experimental work as has been carried out (and much more is wanted), there is general agreement that the paraffins and other non-polar compounds are not absorbed, but that they can be carried through if admixed with other bases which are themselves readily absorbed. Whether it is desirable to carry paraffins through in view of the inability of the body to metabolize them is a matter for consideration, but what can happen to them can be made to happen to medicaments. Harry (1941) summarizes the results of skin-penetration trials as follows (the asterisk is used to denote the relative intensity of absorption).

Oil in water emulsions

Oleic acid ****	
Lard ***	Lard 20% + lanette wax S.X. + water ***
Cod liver oil ***	Lard + triethanolamine + stearic acid + water ***
Wool fat **	
Oleyl alcohol ***	Liquid paraffin + lanette wax S.X. + water **
Olive oil **	Liquid paraffin + lanette wax S.X. no water **
Arachis oil **	Soft paraffin + lanette wax S.X. + water **
Castor oil **	Soft paraffin + lanette wax S.X. no water **
Liquid paraffin *	
Soft paraffin *	

Harry also showed by experiments with solutions of dyes that in neither o/w nor w/o creams, is the aqueous phase absorbed to any appreciable extent, and that in w/o creams the absorption corresponds to that characterizing the oil-phase alone, and a water-soluble dye remains on the skin surface. In o/w creams, evaporation of the film of water results in a residual film of emulsified oil, miscible with the skin sebum and readily re-wetted (i.e. removable by washing with water). If two emulsions are prepared, one w/o and the other o/w, using an emulsifier which is very similar in constitution and with identical proportions of oil and water in the two cases (e.g. 45% oil and water and 10% emulsifier), the products being homogenized to give the same dispersion-size, there appears little difference in absorption or in physical oiliness.

These facts are important and should be borne in mind when constructing formulae. It may not be desirable to leave a residual film of emulsified oil on the skin surface, particularly if the emulsifier is of the new sulphated-alcohol type which is suspected of causing skin reactions. It may not be worth the price of obtaining a water-washable cream, and it may be better to design a w/o cream with a blander emulsifier, such as wool alcohols, which is not very difficult to remove.

On the other hand, the skin condition may be a deciding factor. Thus, it is reasonable to argue that better contact and therefore better penetration is obtained on an excessively dry skin if an o/w emulsion is used, whilst for the seborrheal condition a w/o emulsion might be preferable, avoiding paraffin bases which would only tend to accumulate and cause congestion.

The presence of antiseptics in ointment bases has been the subject of much investigation, and the general conclusions are that phenols are much more active if prepared in o/w emulsions than in an oily base such as paraffin or w/o emulsions. These results, however, were measured on agar-plates, where the phenol had to penetrate an aqueous medium to show its effect. This may not be true evidence, and a different result may be obtained on the skin, as phenol is much more fat-soluble than water-soluble.

The purely oleaginous base, such as lard and, more particularly, paraffin, has been criticized in that

- its greasiness interferes with the radiation of heat from the skin and therefore it should not be used in inflammatory conditions such as eczema,
- it does not mix with or absorb the serous discharge from a wound,
- it is aesthetically disliked by the patient, because of its greasy and clothes soiling character. This is an important point for, given an elegant preparation, the patient will be much more likely to co-operate in treatment.

The pH of the skin, and consequently the pH of the medicating preparation may be important factors in treatment. Some of the new emulsifiers are quite stable over a wide

range of pH and can be adjusted for experimentation. Hence it is essential that the dermatologist should become familiar with these new cosmetic preparations. Their number is large and is rapidly increasing. Those who wish to study the subject more than superficially may rightly be puzzled and disappointed by the nomenclature and the method of marketing the substances, for their names rarely denote their constitution. Indeed few are single chemical substances, but rather mixtures, and this fact alone makes any official adoption of them extremely awkward because of the difficulty of setting up standards. The same fact prevents any reliable controlled clinical trials, for the same proprietary substance can, and has been known to, vary at the whim of the manufacturer. Yet such clinical trials are essential, for so many of the products are entirely new in constitution that any possible reactions following their continued application must be carefully watched. These facts, however, should not prevent their use, for their consumption in cosmetic preparations is large, and this is sufficient reason for proceeding with trials.

The following is a necessarily brief account of some of the more commonly-used substances and their characteristics.

Characteristics of Modern Ointment Bases

Oleaginous Bases

There is little development here beyond the provision of the paraffin bases, lard and the vegetable oils. Oleyl alcohol, the alcohol corresponding to oleic acid and much less liable to rancidity, is worth consideration because it is so readily absorbed and metabolized. Rancidity in any of these substances may be prevented by such antioxidants as ethyl or propyl gallate (Boehm & Williams, 1943) which are neutral and innocuous.

Mucilaginous Bases

Because of the shortage of glycerin during the war many substitutes for glycerin of starch or glycerin pastes, containing tragacanth gelatin, etc., have been tried and, generally speaking, have proved satisfactory. Examples of these are the methyl celluloses under various trade names such as Cellofas W L D, Cellofas W F Z, and PMB444 Tylose Promulsin. These are products of varying composition and, like tragacanth, they form thick mucilages or jellies with water. The quantities to be used vary with the composition. As the substances are cellulose derivatives, they are not so prone to a bacterial and fungal attack as starch and tragacanth, but any added ingredients may support a fungal growth, and they should contain a preservative such as chlorocresol, or phenylmercuric nitrate. They may be used to incorporate a wide variety of medicaments such as phenolic antiseptics (coal-tar included), phenyl mercuric nitrate and other mercurials, skin anaesthetics and astringents. For an account of their use see Swallow & Whittet (1941, 1942) and Whittet (1943).

Sodium alginate is a preparation obtained from seaweed and sold as manucol V. Its properties are similar to those of tragacanth, except that the addition of any calcium salt increases the viscosity of its mucilages. Its uses may be similar to those of methyl cellulose. For further details see Matthews (1942).

Carob gum, sold as such and as hydra gum, is obtained from the seeds of the locust bean. Its use and properties resemble those of tragacanth, except that it contains some heat-coagulable protein (see Knight & Dowsett, 1936).

Emulsifiers and Emulsifying Bases

These may be divided into bases producing w/o (water-in-oil) emulsions and those producing o/w (oil-in-water) emulsions.

1 *Water-in-oil emulsifiers*—Wool fat and wool alcohols are probably the most important. Wool alcohols is a brown wax, representing a purified fraction of wool fat and practically superseding it in use. As *Alcoholia Lanae* it is official in the 6th Addendum of the British Pharmacopoeia. Blended with the paraffins it constitutes *Ung. Alcohol Lanae* of the 6th Addendum. It can be used as such, or it is capable of taking up an equal quantity of water or aqueous solutions. Containing 50% of water it is official in the 6th Addendum as *Unguentum aquosum* (hydrous ointment). Both ointments are useful for a wide variety of medicaments, both water-soluble and insoluble. The sulphonamides have been

so compounded, and it is possible that penicillin would be successful in such a base.

Higher fatty alcohols such as cetyl or stearyl. These are white odourless wax-like solids which, when admixed with a fatty or paraffin base, will emulsify water or aqueous solution in the form of w/o emulsions. Cetyl alcohol has found a place for this purpose in the Swiss Pharmacopoeia. They are rarely used by themselves, but rather to augment the action of wool fat or wool alcohols. A commercial product of this composition is sold as lanette wax.

ii *Oil-in-water emulsifiers*—Sulphated higher fatty alcohols. The usual substance is the sulphated product of a mixture chiefly of cetyl and stearyl alcohols. In appearance it is an off-white wax-like solid which mixes readily with hot water to form a cream. Admixed with a fatty or paraffin base it is capable of emulsifying large quantities of water or aqueous solutions forming an o/w emulsion, the consistency of which can be widely varied. Because water is the external phase, the cream readily mixes with water and can therefore be washed off the skin or off dressings. It is probably the emulsifier which has attracted most attention, being widely used and experimented with under its trade name of Lanette Wax S X. (One should distinguish lanette wax S.X. from Lanette Wax. The former forms o/w emulsions and the latter w/o. The similarity of the names is unfortunate and is the cause of much confusion, particularly in medical literature.) In composition it contains mainly cetyl and stearyl alcohol, together with about 10% of sulphurated products. The important characteristics of the product are

- a The cream formed is of the o/w type
- b It is washable
- c The substance is absorbed by the skin
- d Its emulsions are very stable to a wide range of pH, both acid and alkaline

It is in fact, widely used in the manufacture of cosmetic creams and forms very elegant preparations. A great deal of experience of the medicated creams with this substance has already been obtained and many formulae have been published. Thus Mumford (1938) recommended it as a general base (H E B) compounded as liquid paraffin 3, white soft paraffin 2, lanette wax S.X. 2. This to be medicated either alone or with an aqueous solution (see also Soulsby, 1940). It has also been formulated with sulphamylamide as a burns-dressing with benzyl benzoate and as penicillin cream (*Medical Research Council*, 1944).

Because it has been so widely used, we are beginning to compile certain criticisms of its use. There is evidence that the sulphated fatty alcohols are not always well tolerated on the skin and that some patients are allergic to them. Thus Goldsmith (1940) reports that, while preparations of the Mumford base type were especially useful in treating cases of acute weeping eczema, they were less successful in replacing zinc paste in the treatment of acne vulgaris. He also states that a certain amount of hypersensitivity was exhibited. Burrows & Russell (1945) also report sensitivity of skins to penicillin cream containing lanette wax S.X., and that patch-tests with the wax were positive.

Lanette wax S X seems, moreover, to be a variable product, for it apparently varies in consistency, and from white to yellow in colour. Its actual composition has varied, for it has been marketed as both the phosphated and the sulphated product, each having its special use in cosmetic creams, but such variation is most undesirable in a medicated product when the medicament may not be compatible with both forms. Moreover, it has been reported that, on sterilizing creams by autoclaving as is required in penicillin cream, acidity may or may not be produced. This variability in a product which is potentially so useful is to be regretted, for some such substance must, sooner or later, be standardized and included in the Pharmacopoeia.

Triethanolamine Soaps

Triethanolamine is a commercial article containing about 75% of pure triethanolamine and is used as a substitute for sodium and potassium hydroxide for producing soaps from the higher fatty acids, such as oleic or stearic, for use as cosmetic and medicated creams. Such soaps are more water-soluble than the sodium or potassium types, and the base itself is non-irritating to the skin. The soaps can readily be made less alkaline and therefore more suitable for skin medication. They form excellent o/w creams with

oils but they remain soaps and have the incompatibilities of ordinary soaps Benzyl benzoate is readily formulated with them

Conclusion

In conclusion it should be emphasized that further experience of these new products, particularly controlled clinical

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experience, is required and that they must be produced to a standard specification The success of a particular preparation depends upon a good formulation, and it is in this respect that the dermatologist should ally himself with the pharmacist, who is expert in this work There is no doubt that a combined dermatological and pharmaceutical effort in this field of research will yield most fruitful results

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¹ [see *BMB* 387/51]

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PSYCHOLOGICAL FACTORS IN CUTANEOUS AFFECTIONS A NOTE ON SOME RECENT PUBLICATIONS

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Considerable and increasing interest has been taken of recent years in the physical manifestations of emotional changes, and the opinion has been growing that not only may these manifestations ape those of bodily disorder, but also that well-known clinical syndromes of bodily illness may themselves be caused by psychological factors Exophthalmic goitre was implicated in this way as long ago as during the 1914-18 war and more recently an important cause of peptic ulceration has been sought in worry and stress (Davies & Wilson, 1937) This new "psychosomatic" mode of approach to the problems of general medicine has been perhaps particularly prolific in the field of dermatology

In 1940 Stokes & Beerman published a critical review, with 81 references, on the literature that had then accumulated on psychological aspects of dermatology and allergic illnesses They criticize the conservative attitude of many dermatologists who are inclined to minimize the importance of these aspects, and more particularly the temptation to regard pathological conditions as being due to a single cause The search for a single cause may be an aid to clarity in the early stages of research, but is an oversimplification which has to be abandoned with increasing knowledge In their subsequent discussion they give an account of the physiology of vasomotor phenomena and sweating, and of their central control, of the pruritus mechanism, of "psychoneurogenous allergens", "the allergic personality", the influence of particular emotions, sex and erotic elements, the parent-child relationship The points dealt with are more likely to be of interest to the dermatologist than to the psychiatrist.

Rogerson (1939), in an interesting paper, not only discusses the justification for seeking for psychological causes in many skin conditions, but provides new material of his own In his opinion there is some usefulness in the old classification of humanity into the vagotonic and the sympathetotonic, and with the one state he associates prurigo, dermatographia, and a tendency to lichenification, with the other vitiligo, alopecia areata and scleroderma, both constitutional types may under appropriate stress develop hyperidrosis, and the secondary effects that may result from it. He describes work done by himself on the asthma-eczema-prurigo group, and gives an interesting account of the main features of the personality of children liable to asthma and eczema, in the main they are, he thinks, over-active, over-anxious, irritable, aggressive, ambitious, usually of superior intelligence, and demand much attention from their over-fussed parents, great benefit often results from removing them from what is in fact an unhealthy home atmosphere, or from at least making an attempt to mitigate the extreme solicitude shown by their parents Rogerson also draws attention to the sexual factor in prurigo, associates pruritus ani in the male with homosexual tendencies, and remarks

that scratching the itching spot may procure what is indeed, though it may not be so recognized by the patient, sexual pleasure

Klaber & Wittkower (1939) give an account of a psychiatric investigation of 50 cases of rosacea, controlled by an equal number of patients with fracture They consider that there is a constitutional factor in rosacea which lies in a tendency to loss of contractile power of the smaller blood-vessels of the face Of the rosacea patients, 35, as against 17 of the controls, had a history of uncontrollable blushing as a child Thirty-five of the rosacea patients and only 11 of the controls described themselves as being of quiet and reserved disposition, to which traits the authors would add a high self-esteem and repressed sexual and aggressive tendencies In 36 of the rosacea patients there had been prolonged social anxiety, in 20 prolonged emotional stress, and in 13 a recent acute emotional trauma They discuss at some length the psychodynamics of rosacea

Recent contributions by dermatologists refute the charge laid against them both by Stokes & Beerman and by Rogerson of being blind to psychological influences Hellier (1944) points out that skin affections can usefully be divided into (a) diseases which can be traced to a specific external factor, and (b) skin reactions in which the constitution of the patient is the source of the specificity The tendency to eczema may be manifested in infancy, in one patient it appears after a sore throat or a scratch, in another after a period of worry He agrees with Rogerson in describing eczema patients as over-active, and over-conscientious worriers Psychological factors are important in all pruriginous conditions, in rosacea and lichen planus All cases of alopecia areata are nervous in origin Hyperidrosis is generally associated with chronic anxiety Even warts, though demonstrably due to an infective virus, may be cured by suggestion.

MacKenna (1944) briefly describes the main classifications of personality-type current in psychiatry—the hysteric, the obsessional and the anxious In the hysteric, self-inflicted injuries are particularly frequent, in the obsessional, pruriginous eruptions, often lichenified—neurodermatitis, pruritus ani, diffuse simple prurigo, dermatitis medicamentosa, in the anxious personality, rosacea. Psychological factors are important in dysidrosis, acne, lichen planus, psoriasis MacKenna has been impressed by the psychological unreadiness for war of soldiers suffering from pompholyx, and remarks "The debunked narcissist solves his mental turmoil and escapes from an insupportable position by a skin eruption which is usually of an exudative type" He describes the simple measures of group psychotherapy that may play a large part in the satisfactory running of an Army skin-centre

Much attention has been paid to the selective incidence of skin infestations in men of subnormal intelligence. The first to observe this was Hodgson (1941a, 1941b) In his first

paper he reports the results of intelligence tests in 100 scabietic soldiers and in 500 unselected RAMC (Royal Army Medical Corps) personnel Whereas 5 % of the RAMC men were of poor intelligence, 27 % of the scabies patients fell into this group , and the upper two of his intelligence groupings included 76 % of the RAMC men, 33 % of the patients In his second paper he gives, in the table quoted below, the ratings on the "progressive matrices " of 1,002 patients attending a military dermatological clinic

INTELLIGENCE					
	No	very inferior	below average	average	above average
Control cases	500	5 %	19 %	50 %	26 %
Skin diseases	306	5 %	28 %	53 %	14 %
Infestations	497	18 %	38 %	38 %	6 %
Venereal disease	199	17 %	33 %	37 %	13 %

He concludes that the patients with skin diseases are probably a normal selection from the point of view of intelligence, but that both the men with skin infestations and those with venereal diseases are inferior

Hodgson's work has been criticized by Mellanby, Northedge & Johnson (1942) In their opinion the RAMC personnel rated too high to be a fair sample, and they themselves use Army norms based on several hundred thousand men , they find no marked deviation from Army standards in 288 scabies patients, and no differences between those men reporting sick and those discovered on routine inspection, those with heavy and those with light infestations, or those with and those without secondary infection

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Despite these contradictions in the evidence, it seems probable that there is an association between poverty of intelligence and liability to skin infestation MacKenna (1943) quotes results given by Hargreaves and based on a very large Army material The scabies incidence in men of high intelligence (S G 1) was 0.5 %, in men of low intelligence (S G 5) 2.2 %, with a continuous rise from the lower to the higher of these figures in the intervening grades Rollin (1943) has also reported in detail intelligence findings in 312 members of the WAAF (Women's Auxiliary Air Force) found to have pediculosis capitis, and 312 in whom this was not found The test used was the "G V K " (devised by Dr W Stephenson, of Oxford), which provides tests of general intelligence, verbal ability and practical ability In the 0th to the 50th percentiles of the standardized test, i.e below the half-way point in the scores, separately recorded for G, V, and K, were found 69 %, 76 % and 96 % respectively of the infested WAAFs, 28 %, 36 % and 71 % of the uninfested

These associations between skin infestation and intelligence are not of great theoretical interest, though they may be of considerable practical importance One can hardly think of the finding as implying more than that the less intelligent of the community are less able to protect themselves against infestation, less likely to observe a satisfactory skin toilet The associations between particular types of personality and types of skin eruption, if confirmed and developed by further work, are much more interesting, and may ultimately give us increased insight, not only into the pathogenesis of abnormal skin reactions, but also into the central control of somatic physiological processes in general

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REVIEW OF SELECTED PAPERS

Numerical Studies of Acne

739

THE INCIDENCE AND LOCALIZATION OF ACNE
by E L Cohen, *British Journal of Dermatology and Syphilis*, 57, 10-14, January-February 1945

The incidence of acne in children and adolescents has been the subject of a number of investigations, but the incidence in young adults has not received sufficient attention

An investigation was carried out on 500 young women The presence or absence of acne was noted and its site—chin, face (excluding chin region and including forehead) and trunk—was recorded Acne that could be seen on simple inspection was defined as "clinical acne" Occasional comedos which were not immediately apparent were described as "slight acne" Clinical acne plus slight acne make "total acne" incidence The patients were from 17 to 40 years of age, 97 % being under 30 The average age was 21

The incidence of acne at all the ages was

	Chin		Face		Trunk		Total	
	Tot	Clin	Tot	Clin	Tot	Clin	Tot	Clin
Number	243	103	107	54	162	94	343	168
Percentage	49	21	22	11	33	19	69	34

Tot = Total acne, Clin = Clinical acne

It will be seen that the chin is by far the commonest site for acne, the incidence being approximately twice as great as for the rest of the face, including the forehead

The percentages with total acne and with clinical acne in different age-groups were

Age	Chin		Face		Trunk		Total	
	Tot	Clin	Tot	Clin	Tot	Clin	Tot	Clin
17-18	47	19	24	11	26	13	62	30
19	51	30	39	26	32	19	73	43
20	45	17	30	17	35	21	64	34
21	57	27	18	7	35	22	75	37
22	52	19	12	7	35	16	70	30
23-26	44	16	28	16	26	14	65	33
Over 27	26	8	8	5	27	16	50	21

The differences with age were examined by the X² test (Hill, 1942)

The ages of 121 men with clinical acne, seen in skin departments, were recorded Their ages varied from 18 to 44 years Twenty-five per cent were above the age of 25, and 9 % were 30 or more

The author concludes from this and a previous (Cohen, 1942) investigation that most writers put the age-limit of acne too low The chin region was by far the commonest site of acne in the group of women investigated

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THE RELATIONSHIP OF ACNE WITH DANDRUFF AND SEBORRHOEIC DERMATITIS

by E. L. Cohen, *British Journal of Dermatology and Syphilis*, 57, 45-47, March-April 1945

Many authors regard acne as a complication of seborrhoea. Mumford (1933) found increased sebaceous secretion in 100 young women with acne. In the cases reported by Somerford (1933), 42.1% of the men and 50% of the women had "definite seborrhoea," and 60% of the men and 80% of the women had localized "greasiness of the skin." Stokes & Sternberg (1939) comment on seborrhoea and comedoformation following encephalitis, and on the "high grade seborrhoea associated with depressive episodes in young women." They quote Unna as saying that effective treatment of seborrhoea of the scalp is necessary for lasting benefit to acne.

An investigation was carried out on 500 women whose average age was 21. 97% of them were under 30. The amount of dandruff was noted and at the same time a search was made for seborrhoeic dermatitis. Table I shows the incidence.

TABLE I

	Dandruff		Seborrhoeic dermatitis
	O	++	
Number	73	74	58
Percentage	15	15	12

O = no dandruff, ++ = much dandruff

These conditions were then tabulated in relation to acne at different sites and expressed as percentages.

TABLE II

	Chin		Face		Trunk		Total	
	Tot	Clin	Tot	Clin	Tot	Clin	Tot	Clin
Dandruff O	38	14	18	11	29	14	62	27
Dandruff ++	59	26	24	19	31	20	74	36
Seb. derm.	43	16	9	5	26	12	59	26
All cases	49	21	22	11	33	19	69	34

Seb. derm. = seborrhoeic dermatitis, Tot = total incidence of acne, the presence of any comedones being regarded as signifying acne, Clin. = "clinical acne", i.e. acne that can be seen at a glance without searching for comedones.

The statistically significant figures here are those showing a greater incidence of total acne of the chin when there is gross dandruff and, surprisingly, the lower incidence of acne of the face in conjunction with seborrhoeic dermatitis than in the whole series.

The figures produced in Table II confirm the well-recognized relationship between acne and gross dandruff. The comparatively small incidence of acne in those with seborrhoeic dermatitis is surprising. This is contrary to the views of Pillsbury, Sulzberger & Livingood (1942), who write that these conditions are apt to co-exist, but they were writing principally about men and it is a clinical impression that is true of men and not of women. Nevertheless this finding is difficult to explain if acne and seborrhoeic dermatitis have a common background.

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PSYCHOGENIC FACTORS IN ACNE

by E. L. Cohen, *British Journal of Dermatology and Syphilis*, 57, 48-57, March-April 1945

A thorough review of the literature suggests that there may be a psychogenic factor in the aetiology of acne. With a view to testing this assumption, 90 men were examined by the mosaic test as designed by Dr. Margaret Lowenfeld. Of these, 60 had acne and 30 were controls.

The test material consisted of a box of mosaic pieces in 5 colours and 6 shapes, each shape being available in each

colour. The man was given a wooden tray covered with an accurately fitting piece of paper. The mosaic pieces were demonstrated to him and he was told to do anything he liked on the tray with them. There was no time-limit. The resulting patterns were copied with coloured pencils on to the paper and were sent to Dr. Lowenfeld with no indication as to which were from acne patients and which from controls. She classified them and sent back a report on each. On comparing the results, no significant difference was found between the two groups.

Twenty-nine men and 21 women with acne were interrogated. A brief psychological history was obtained from each. A history suggestive of an emotional disturbance immediately preceding the onset of the acne or of emotional maladjustment was found in 18 of the men and 12 of the women. Among the men these factors were found much more frequently in those over the age of 25 and in those who were married.

The author suggests that the psychogenic factor may be important in prolonging acne than in initiating it. There was a strong clinical impression that women in the thirties with acne were neurotic. There is some evidence that acne may appear shortly after a period of strain or excessive fatigue.

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THE RELATIONSHIP OF ACNE AND HYPERTRICHOSIS

by E. L. Cohen, *British Journal of Dermatology and Syphilis*, 57, 102-106, May-June 1945

A review of the literature shows that there are a number of factors common to the aetiology of acne and hypertrichosis. These conditions are apt to occur together, especially in suprarenal cortical tumours, arrhenoblastomata, and androgen therapy. Milanés (1937) and Pedersen (1942) both claim that hypertrichosis is common in women suffering with acne.

Five hundred women were examined. Their ages were from 17 to 40 years, the average being 21. 97% were under 30. Acne and hypertrichosis were noted. Those with any comedones were said to be in the group of "slight acne", those with lesions seen on simple inspection without searching were said to have "clinical acne". The term hypertrichosis was restricted to (i) obvious hair along the whole of the upper lip, (ii) obvious hair on the chin, or (iii) a hairy chest; it was found in 7% of the women. The incidence of "total acne," "clinical acne," and acne of the chin, face, and trunk taken separately, was lower among those with hypertrichosis than in the whole series, but the differences were not statistically significant.

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Chemotherapy Sulphonamide Rashes

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SULFONAMIDES IN DERMATOLOGY

by D. M. Pillsbury, *British Journal of Dermatology and Syphilis*, 56, 68-80, March-April 1944

The author discusses local sulphonamide therapy in regard to (a) its effectiveness in various septic skin conditions, (b) its effect on the bacterial flora of the normal and abnormal skin, (c) the influence of the vehicle of application and of the particle size of the sulphonamide, and (d) sensitization phenomena due to the local use of sulphathiazole.

He emphasizes the present rather confused nomenclature of the various skin infections and in judging the relative effect of sulphonamide therapy on dermatoses due wholly or in part to bacterial action has employed the following general grouping:

1. Primary acute superficial infections (Impetigo superficial acute ecthyma, acute infectious eczematoid dermatitis, Bockhart's follicular impetigo). In this group the results of

local sulphathiazole therapy are superior to any of the commonly used methods of treatment. The importance of the technique of treatment is emphasized, viz thorough cleansing of the affected site with soap and water once daily, application of the drug three times daily, limiting of the period of treatment to five days so as to avoid the risk of sensitization. If no improvement has occurred within 72 hours it is advisable to change to some other form of treatment.

ii *Acute superficial pyogenic infections occurring as a complication* of such dermatoses as eczema, fungous infections, dermatitis venenata, seborrhoeic dermatitis, insect bites, and lichen simplex chronicus. In such conditions it is important to try and cure the secondary infection as soon as possible, otherwise the invading pathogenic bacteria may become permanent members of the skin flora of the affected site and the patient may become sensitized to such surface bacteria very rapidly. In this group local sulphathiazole therapy was successful in about 50 % of cases in the author's experience—a distinctly inferior result to that obtained in impetigo.

iii *Chronic eczematous lesions* in which local pyogenic infection plays a variable role. The degree to which infection is contributing to the process is often difficult to assess. An example of this group is seborrhoeic dermatitis, with retro-auricular or other intertriginous involvement of the skin. Some cases of nummular eczema, and of occupational dermatitis and atopic dermatitis, can be included in this group. Such conditions are notoriously unstable and in them the risk of sensitization to the application of sulphonamides is great.

iv *Ulcers*. Factors other than local infection, e.g. syphilis, diabetes, or local vascular changes, should first be excluded. The bacterial studies should also include cultures under anaerobic conditions, because the finding of a micro-aerophilic streptococcus means that local sulphonamides will be useless. Otherwise, in suitable cases packing of the ulcer with sulphathiazole or sulphadiazine ointment or powder was moderately successful.

v *Chronic infections of the pilosebaceous apparatus*. When deep infection of the hair-follicle has occurred, the results of local sulphonamides are uniformly disappointing.

The emulsion type of base was found to be superior to an all-grease or paste one as a vehicle for sulphonamides. Sulphathiazole proved superior to sulphadiazine, and both of them are decidedly superior to sulphapyridine.

With regard to sensitization, in acute superficial pyodermas, providing the period of application is not longer than 5 days, reactions are not likely to occur with any frequency or severity. In chronic dermatoses, on the other hand, sensitivity may easily be induced by local application of sulphonamides, particularly of sulphathiazole.

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IMPETIGO CONTAGIOSA. Its Cause and Treatment

by J W Bigger & G A Hodgson, *Lancet*, 1, 544-547, 1/5/43

This paper, by a bacteriologist and a dermatologist of the British Army, records the results of an investigation into the bacteriology of impetigo contagiosa, a "disease characterised by the occurrence of discrete thin-walled vesicles and bullæ which dry to form yellowish adherent crusts and heal without scar."

Two hundred and thirty cultures were made, on blood agar and on blood agar containing 1/500,000 gentian violet (for the isolation of streptococci), from the impetigo lesions occurring in 125 men and 5 women serving in the British forces.

Staphylococci and hæmolytic streptococci were isolated much more frequently than any other bacteria. Ninety-five per cent of the staphylococci coagulated human plasma (*Staph pyogenes*). Eighty-six per cent of the hæmolytic streptococci belonged to Lancefield's group A (*Strept pyogenes*). Staphylococci were present in 97.0 % of the cultures, in 67.0 % without *Strept pyogenes*. *Strept pyogenes* was present in 32.2 % of the cultures, in 2.1 % without staphylococci. Fluid from 17 vesicles of 10 patients yielded pure cultures of *Staph pyogenes*.

The longer the condition had lasted, the higher was the proportion of cases which yielded *Strept pyogenes*. This organism was isolated from 22 % of the lesions which had

been present for less than 8 days and from 77 % of lesions which had been present for more than 35 days.

Eighty-one cases were treated, after mechanical removal of crusts, with sulphapyridine or sulphanilamide applied locally with a protective paste. Seventy-five of these were cured in an average of less than 10 days. The results in 19 cases treated with protective paste without sulphonamide were almost as good. Fourteen cases were treated, without medication, by mechanical removal of crusts, the raw areas being covered with dry sterile dressings. All were cured in from 5 to 17 days (mean 9.8 days).

The authors believe that sulphonamides are of use mainly in preventing complication of the disease by infection with *Strept pyogenes* or in curing such infection. The essentials of treatment are removal of crusts, prevention of extraneous infection, and avoidance of irritating medication.

Inoculation of human volunteers with fluid from vesicles, fluid from oozing lesions, and cultures of *Staph pyogenes* occasionally produced lesions resembling those of impetigo, but the authors did not consider themselves justified in concluding that they had produced true impetigo by any form of inoculation.

In their opinion, impetigo is rarely, if ever, caused by streptococci of any type but is due to *Staph pyogenes* acting either alone or, more probably, in conjunction with some other factor. This factor may be a virus, a particular degree of susceptibility or immunity, the presence of some abnormal metabolite, or the absence of some essential food substance.

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IMPETIGO CONTAGIOSA TREATED WITH MICROCRYSTALLINE SULPHATHIAZOLE

by J W Bigger & G A Hodgson, *Lancet*, 2, 78-80, 15/7/44

Fifty cases of uncomplicated impetigo contagiosa were treated with microcrystalline sulphathiazole, supplied as a 15 % suspension in normal saline. A further 25 cases treated with a 15 % suspension of ordinary sulphathiazole, served as a control.

Of the 50 cases treated with microcrystalline sulphathiazole, 48 were cured in an average of 5.3 days. Of the 25 cases treated with sulphathiazole, 23 were cured in an average of 6.5 days. The serous discharge usually ceased within 1-2 days of application of microcrystalline sulphathiazole and the epithelium rapidly regenerated. Cure was sometimes delayed by the appearance of fresh lesions. The organisms found in the lesions seldom disappeared before healing was well advanced. Only one patient treated with microcrystalline sulphathiazole developed sensitivity to the drug.

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SKIN ERUPTIONS DUE TO THE LOCAL APPLICATION OF SULPHONAMIDES

by G A G Peterkin, *British Journal of Dermatology and Syphilis*, 57, 1-9, January-February 1945

This is a review of 65 cases, under the author's care in North Africa, of cutaneous sensitization reactions to one or other of the sulphonamide drugs applied externally for conditions such as wounds and burns, impetigo, impetiginized seborrhoeic eczema, and "running ears." In 61 of the cases the first sulphonamide to be applied was sulphanilamide powder.

In the milder cases the reaction consisted of a maroon-coloured erythematopapular rash on the exposed parts of the body, but in the more severe type the skin, particularly of the face, became oedematous with an associated photophobia, cheilitis, glossitis, stomatitis, and rawness of the scrotum. Sometimes the eruption was vesicular or bullous and the patients were pyrexial and toxic.

As the majority of cases had been treated originally with sulphanilamide powder, the author suggests that their skin had been sensitized by absorption of the sulphanilamide through the respiratory system. Subsequent exposure to sunlight, one infers, was considered to be the precipitating factor, though the author does not record to what extent these patients were exposed at the time of their treatment and in the 4 case-histories given there is no mention of any coincidental exposure to sunlight.

In contrast, of a series of over 200 cases of skin infection treated with 5 % sulphathiazole in Lassar's paste or lanette

cream and subsequently exposed freely to sunlight, in only one patient, who had been previously treated with sulphanilamide powder for impetigo, did a mild eruption develop which was limited to the exposed areas. No skin-reactions were observed in a smaller series treated with 10% sulphanilamide in Lassar's paste.

The author therefore urges that powdered sulphonamides should not be applied to the skin for minor conditions.

As regards prognosis and duration of photosensitivity, he was unable to follow up all the patients, but states that most were discharged from hospital perfectly able to tolerate the strong sun of North Africa. Ten patients who were able to report over a period of 2-3 months had kept well.

SULPHONAMIDE RASHES An Analysis of 500 cases seen in North Africa and Italy

by G. A. G. Peterkin, *British Medical Journal*, 2, 1-6, 7/7/45

In just under two years' service (1943-44) in North Africa and Italy, the author saw more than 650 cases of cutaneous sensitivity to sulphonamides, from which his series of 500 cases is drawn. A much greater incidence of sulphonamide sensitization to light was, of course, to be expected than that encountered in Great Britain. His figures are even higher, however, than those reported from the Middle East (Park, 1943, Tate & Klorfajn, 1944a, 1944b). This is attributed to the increased use of sulphonamides in active theatres in the treatment of wounds, burns and septic conditions.

Many cases followed systematic administration, after the skin had already been previously sensitized by local applications of sulphonamides. Of the various drugs used, sulphathiazole seemed to be the most frequent offender, though sulphapyridine, sulphadiazine or sulphaguanidine were responsible for other cases. Sulphanilamide powder (which had been used in over 90% of the cases) seemed more likely to cause reactions than the same drug in the form of a cream or paste.

The author classifies the great variety of sulphonamide eruptions observed into 16 groups

	No	%
i. Sulphonamide—light	361	72.2
a. Erythematous-papular	47	9.4
b. Vesicular	1	0.2
c. Severe—bullous, crusted, and oedematous	309	61.8
d. Telangiectatic	4	0.8
ii. Contact Vesication, followed by weeping and superficial ulceration, may be general eczematization	51	10.2
iii. Infectious eczematoid dermatitis, following a contact dermatitis	31	6.2
iv. Disseminated neurodermatitis—may be secondary to a patch of neurodermatitis	4	0.8
v. Generalized vesicular	4	0.8
vi. Generalized bullous (pemphigoid)	1	0.2
vii. Fixed type of drug eruption	1	0.2
viii. Purpuric		
a. Generalized—after oral administration	1	0.2
b. Contact—purpuric reaction	3	0.6
ix. Morbilliform. Often with vesico-bullous eruption of hands and feet	12	2.4
x. Scarlatiniform	3	0.6
xi. Urticarial	3	0.6
xii. Lupus erythematosus	5	1.0
xiii. Erythema multiforme	6	1.2
xiv. Erythema nodosum	5	1.0
xv. Pustular or acneiform	4	0.8
xvi. Exfoliative dermatitis	5	1.0

He also describes other cases resembling severe impetigo, as well as a chronic form, the appearances of which could not be distinguished from those of seborrhoeic dermatitis. A careful history, however, elicited the use of sulphonamides, and exacerbation on exposure to light affecting the face, neck, hands, arms and knees.

Illustrative descriptions are given of each type of eruption, of which the "sulphonamide-light" group was by far the most common, and the intensity of the reaction, of a degree seldom seen in Great Britain.

A high proportion of these patients had been treated with sulphanilamide powder for impetigo. The source of the subsequent bullous eruption was often undiagnosed before their admission to hospital, and many were thus treated with large quantities of sulphonamide tablets with deplorable

results. It was relatively easy to desensitize these cases, by the use of very small doses, gradually increased. This, however, had no influence on the course of the eruptions resulting from photosensitization.

It was found that the use of any of the flavines aggravated the eruption, confirming the work of Russell & Beck (1944), who showed that sulphonamide-proflavine mixtures enhanced the toxicity of both drugs.

The incidence of sulphonamide reactions in United States Forces, in the same theatre, seemed very low by comparison. This is attributed to the local use of 5% sulphadiazine cream, in preference to any other form or preparation, and the rare use of acriflavine.

The most important features of the early treatment of the "sulphonamide-light" group were the avoidance of exposure to sunlight, and the frequent application of wet dressings, of dilute lead, zinc, or copper salts. Penicillin in dosage ranging from 500,000 to 1,250,000 units proved useful in the most severe septic types of photo sensitization, and in the single case of pemphigoid type encountered.

Two years ago the authors (Peterkin & Jones, 1943) reported favourably on the use of 5% sulphathiazole cream or paste in the treatment of impetigo, with only 1% of cases of sensitization. In view of his subsequent experience, he now considers the use of any kind of sulphonamide unjustified in this condition.

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SULPHANILAMIDE DETERMINATION IN SPONTANEOUS AND CANTHARIDIN BLISTERS IN VESICULAR AFFECTIONS OF THE SKIN (PEMPHIGUS, DERMATITIS HERPETIFORMIS, HERPES GESTATIONIS, EPIDERMOLYSIS BULLOSA HEREDITARIA)

by A. Dostrovsky & F. Sagher, *British Journal of Dermatology and Syphilis*, 57, 85-96, May-June 1945

Sulphonamides have a marked curative effect upon certain skin conditions such as pemphigus vulgaris and dermatitis herpetiformis. Dostrovsky & Sagher, working in the dermatological department of the Rothschild-Hadassah University Hospital, Jerusalem, investigated whether these compounds had any special tendency to accumulate in the skin or whether the concentration therein was dependent on that of the blood. For this purpose they gave sulphonamides to 7 patients (3 with pemphigus, 2 with dermatitis herpetiformis, 1 with herpes gestationis and 1 with epidermolysis bullosa), and made simultaneous estimations of the concentration in the blister-fluid and in the blood. They found that the concentration of sulphonamide in the blister-fluid was approximately equal to that in the blood, although there was a certain time-lag, the rise and fall of the concentration in the blisters being several hours later than that in the blood. The level with sulphapyridine, sulphathiazole, sulphanilamide and sulphaguanidine, during rather low therapeutic courses, usually ranged from 0 to 6 mg. per 100 cm.³, with sulphadiazine the level reached was a little higher. When the administration of sulphonamide ceased, the compound disappeared rapidly from both blood and blister-fluid, and usually little or none was found 60-84 hours after the last dose. It is clear that sulphonamides diffuse readily from the blood into the fluid of blisters and conversely. Observations on artificial blisters made by applying cantharidin to the skin of controls yielded similar results.

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A NOTE ON A CASE OF BLASTOMYCOSIS CURED BY SULPHAPYRIDINE AND SULPHATHIAZOLE

by M. Albert, *British Journal of Dermatology and Syphilis* 55, 294-296, December 1943

Cutaneous blastomycosis is a rare disease in Britain. The case described occurred in a man aged 50 years. During

the war of 1914-18 he received a shrapnel wound of the left ankle, which did not involve the bone and which healed with a keloid scar. This broke down in August 1941. Lesions appeared on the left leg and spread to the right groin and the left elbow. These lesions consisted of areas of violet-red granulation tissue, heaped up in some places and ulcerated in others, with numerous small cutaneous abscesses spreading centrifugally. There was no evidence of systemic spread.

A diagnosis of blastomycosis was made in November 1942, by culture on Sabouraud's medium and by biopsy.

All local treatment, including x rays, had failed. Intensive potassium iodide medication was also ineffective. Sulphonamides were administered as follows:

- | | |
|--------------------|-----------------|
| i Sulphapyridine | 80 g in 16 days |
| 14 days' rest | |
| ii Sulphathiazole | 70 g in 16 days |
| 14 days' rest | |
| iii Sulphathiazole | 36 g in 8 days |

The rash healed completely. The local dressing employed throughout the sulphonamide treatment was a 12½% solution of sodium sulphate. This was not in itself effective, as there was no evidence of healing during the "rest periods."

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THE TREATMENT OF SYCOSIS BARBAE BY PENICILLIN CREAM

by A Burrows, B Russell & H B May, *British Journal of Dermatology and Syphilis*, 57, 97-101, May-June 1945

Sycosis is defined as a chronic staphylococcal folliculitis of the beard area and may be divided into two main types, the straightforward folliculitis and the seborrhoeic type, which is an obvious extension of seborrhoeic dermatitis. It has long been known to be one of the most intractable disorders of the face, and almost all treatment, including temporary epilation by x rays, has proved unsatisfactory. General light baths given 4-6 times a week over prolonged periods are helpful in some cases.

An investigation was carried out on 21 cases in whom the duration of infection varied from 14 years to 8 weeks. In all cases a bacteriological examination was made of the pus from an infected hair follicle. A primary culture was made on to plasma agar (Penfold, 1944) and from this, sensitivity of the organisms was tested by the antiseptic cream method (May & Stern, 1945).

When the predominant organism was penicillin-sensitive, treatment was carried out with penicillin cream containing 200 units of penicillin per g. It is essential to instruct the patient carefully in the technique of the aseptic handling of the cream, which should be extracted from the container with a sterilized knife-blade or spoon, spread on clean lint, and applied thinly to the affected area 2 or 3 times a day. Patients should return at intervals of not more than 2 weeks for fresh supplies of cream or potency-tests on their own supply.

Nineteen of the cases in this series were caused by a penicillin-sensitive strain of staphylococcus. Of 13 cases of more than 1 year's duration, 6 were free from the infection in an average time of 6 weeks, and 6 were improving over an average period of 6 weeks. Of 6 cases of less than a year's duration, 4 were clear in an average time of 2½ weeks and one was improving over a period of 5 weeks. No improvement resulted from the treatment of 2 cases due to insensitive strains of bacteria. One case due to penicillin-sensitive staphylococci improved only very slightly. The culture in this case showed the growth of a *Proteus* which had an inhibitory action on the penicillin.

To lessen the tendency to relapses:

- i Apply the penicillin cream to the anterior nares as well as to the skin of the beard area
- ii Treat nasal discharges, blepharitis, or otitis media or externa, if present
- iii Treat any other manifestations of the seborrhoeic state
- iv Eliminate foci of sepsis in throat, teeth and sinuses
- v Continue treatment for a few weeks after apparent cure
- vi Use the cream prophylactically after relapses, or if nasal swabs remain persistently positive

vii Instruct the patient to discard his infected shaving brush and face-flannel, or sterilize them by boiling, or to use a brushless shaving-cream

viii Consider in severe cases the use of x-ray epilation in conjunction with penicillin

The authors intend to publish the result obtained in the above cases after a year.

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Contact Dermatitis

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RESPIRATOR DERMATITIS

by J Petro, *British Medical Journal*, 1, 631-634, 23/5/42

The author describes a form of rubber dermatitis due to the wearing of certain types of military respirator. The term "rubber dermatitis" is misleading, because rubber itself is not the allergen responsible, but becomes such in the process of cure and vulcanization in which irritant substances known as "accelerators" and "anti-oxidants" are used.

Sixteen cases of facial dermatitis among personnel at a Royal Naval Depot were investigated. The types of mask owned by the 16 patients were all found to be of a manufacture in which one or other of these irritant compounds had been used. The degree of perspiration proved to be an important predisposing factor.

Lesions were at first confined to areas of the face which came into close contact with the mask, but in some cases extended to the lax tissues round the eyes and in the submental region, appearing in the form of an oedema. The early stage was an erythema, followed by a vesicular and weeping stage. When this subsided the lesions became dry and scaly and finally gradual desquamation occurred. In 4 cases deep-seated submental indurations followed the early submental oedema. The oedema round the eyes was sometimes followed by pronounced swelling of the lids. A mild angular conjunctivitis was observed in 2 cases.

Treatment was empirical, by various applications of which the author gives particulars. Phenobarbitone was given as a sedative.

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DERMATITIS FROM WEARING ARMY SPECTACLES

by W O G Taylor & A G Fergusson, *British Medical Journal*, 2, 40-42, 14/7/45

The authors report 6 cases of dermatitis from army spectacles, all of which were seen in the course of three months. The spectacle frames are made of an alloy of nickel, copper and zinc, known as "nickel silver", plated with nickel. It was concluded that the dermatitis was an allergic phenomenon resulting from a prior electrolytic battery action which ionizes some of the nickel in the presence of the acid sweat and dissimilar metals, aided by body heat. When the sweat, which is an electrolyte, acts upon the base metal, salts are formed and such action is more pronounced in the presence of heat. It is probably a salt of the nickel that causes the irritation.

All cases reported that they sweated freely. The wearing of a respirator, of course, induces free perspiration under the rubber. From all points of view the most satisfactory solution was the adoption of the "respirator wafer" (Taylor, 1944) which gives correction during the wearing of the respirator, and of gold or steel frames at other times. When the refractive error is too high for satisfactory correction by a wafer, the frames should be covered with cycle-tyre valve tubing pulled over the flexible ear-curls and pads, xylonite half-rings clipped over the rims, and jaconet covers stitched over the flat sides.

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DERMATITIS FROM EXPOSURE TO TEAR GAS

by J T Ingram, *British Journal of Dermatology and Syphilis*, 54, 319-321, December 1942

A case of acute bullous erythematous dermatitis in a male adult is described. The condition appeared 6 to 7 hours after exposure to tear gas in a building, during the course of a military exercise. The flexures were mainly affected. The lesions resolved completely in a fortnight under treatment with baths and calamine lotion.

Contact as long as a fortnight later with a steel helmet that had been directly exposed to the gas, produced a reaction within the course of an hour. There were no other ill effects in this case.

TEXTILE DERMATITIS

by J H T Davies & A N Barker, *British Journal of Dermatology and Syphilis*, 56, 33-43, February, 1944

From observations covering a period of 18 months in the dermatological wards of a large military hospital, the authors collected records of 201 cases of dermatoses due to intolerance of the skin to contact with woollen textiles.

Semenology In general, the parts chiefly affected are the lower extremities and forearms, but in some cases the whole covered surface of the body is involved. The clinical appearances are divided into the following main types.

i. Pruritus (18 cases, 9%) Though not always limited to areas in direct contact with khaki or other woollen garment, this disappears gradually while the patient is in bed or clad in cotton or linen clothing, but returns as soon as khaki clothing is resumed, or after exertion sufficient to cause sweating in it.

ii. Erythema (26 cases, 13%)

iii. Erythematous dermatitis (49 cases, 24%) This included 3 cases of a generalized exfoliative erythrodermia.

iv. Eczematoid dermatitis (18 cases, 9%)

v. Circumscribed and diffuse lichenification (8 cases, 4%)

vi. Facial eczema (10 cases, 5%) This was provoked by sleeping in blankets, but in four cases patch-tests with blanket were negative, and experimental inhalation of blanket-dust produced no reaction. This eruption had the morphological characters of an infected seborrhoea, and the distribution strongly resembled that of infantile facial eczema.

vii. Prurigo simplex (4 cases)

viii. A purely urticarial eruption in 3 cases

ix. In one patient, with a long history of intolerance to woollen materials next to the skin, an acneiform and pustular reaction was provoked on the neck by wrapping it in a strip of khaki serge.

x. Prurigo simulating scabies (58 cases, 29%) It seems probable that in this—by far the most important—group, every case began as scabies, but there was no means of knowing the date of the last active infestation. The observed effect of wearing wool next to the skin left no doubt of its contribution to causation, though patch-tests were commonly only faintly positive and cases tended to recover with lapse of time. The eruption is identical with the severest forms of scabies, but, unlike the latter, it increases in intensity towards the ankles, and itching is nearly as severe by day as by night.

Aetiology The authors believe that all these types of eruption are mainly due to intolerance of the skin for wool, they give detailed results of patch-tests and the khaki-tolerance test (K.T.T). The general physical characteristics of 135 cases were recorded of these 66, in which some degree of gonadal deficiency was believed to play a part, are described in some detail, the remainder are briefly classified. Details are given of 42 sugar-tolerance curves, which did give significant information. The possibility of a nutritional deficiency, with particular reference to vitamins C and B is considered, but administration of these vitamins was found to have little or no value in severe cases, though at an early stage in the investigation, a number of cases seemed to respond dramatically to vitamin C. No attempt was made to assess the neurotic factor in view of the high proportion of dermatological patients who exhibit signs of nervous instability. There were very few cases of the usual types of sensitization dermatitis.

Pathogenesis Sensitization may occur spontaneously, or as the result of friction by garments in association with sweating, but more commonly its onset is determined by

some other dermatosis. In 54 of the 89 cases in which the determining factor was recorded it appears to have been scabies. The acquisition of an A V (anti-vermin) battle-dress was apparently blamed by the patient in only 23 instances, but this seems too low a figure. That A V impregnant is not a universal irritant was demonstrated by negative patch-tests given by a series of 50 patients not suspected of sensitization to clothing. The eruption maintained by intolerance of woollen textiles showed a marked tendency to resemble the condition that originally provoked the sensitization. One great difference between this and ordinary forms of sensitization to external irritants, is that with lapse of time patch-tests may cease to give positive results, and patients who have not completely recovered are occasionally able to wear khaki again without delaying complete recovery.

Diagnosis The patient complains of itching, and usually blames his blankets, though the onset of his symptoms may be associated with various other causes. The authors give details of patch-tests and their results. Where these were negative, the K.T.T., which is described in detail, was performed.

Differential diagnosis Four types of eruption might be confused with those under consideration. Dermatitis from dyed clothing is easily distinguishable by its characteristic distribution, another eruption was found to be due to sensitization of the skin to some product of the *Staphylococcus aureus* in sweat-soaked clothing, no light could be thrown on the pathogenesis of a third, which corresponded to the second type described above, but had, in addition, a purpuric element, but patch-tests and K.T.T. were negative, and the eruption was further differentiated by the fact that it extended to previously unaffected skin, while earlier lesions were fading, and that, in addition to severe pruritus, the skin feels tender and movement in the flexures is painful, the fourth condition consisted of scabious eruptions which persisted after disinfestation and gave neither patch-test nor K.T.T. reactions.

Treatment This consists in removal of the irritant, application of simple remedies, such as calamine lotion or liniment, covering pyodermatic lesions with elastoplast, the avoidance of sweating, and, where necessary, the compulsion of sleep by paraldehyde. The authors' general impression is that lapse of time is the most important factor.

Prognosis Cases of long standing, with strongly-positive patch-tests, must be regarded as incurable, mild cases recover slowly when protected by cotton and excused heavy physical exertion, moderately severe cases do not recover completely, but may be returned to duty if protected by cotton without necessarily becoming worse. Unfortunately, as a general rule, they relapse.

CONTACT DERMATITIS IN A MORPHINE FACTORY

by S E. Dore & E W P Thomas, With an Account of the Occurrence of "Morphua Rash" in the Manufacture of Morphine Salts from Opium, by G C. Green, *British Journal of Dermatology and Syphilis*, 56, 177-186, July-August 1944

Occasional reports have appeared in the European and American literature of contact dermatitis from opium derivatives, e.g. in nurses or morphine workers, but otherwise this subject has received little attention and the authors of the present article were unable to find any case-records in the British literature. They have, therefore, reported on 9 cases of dermatitis that occurred at the same morphine factory near London during the period December 1941 to March 1943.

Of these cases, 7 were men (out of a total of 16 men employed) and 2 were women (all the women employed). The average time between commencing employment and the appearance of a rash was 14½ weeks. The distribution of the cases through the various process operations was as follows: Operation 4 (evaporation, crystallization and purification of Gregory salt), 1 case. Operations 5 and 6 (separation of alkaloids, purification of separated morphine salt), 3 cases. Operation 7 (drying, milling, and packing of morphine salts), 5 cases.

In practically all cases the eruption began as an irritable erythematous dermatitis of the eyelids and surrounding area and was sometimes accompanied by quite severe local oedema. The regions next oftenest affected were the nape

of the neck and below the chin in women, and the collar-area in men. Except for one case in which the eruption eventually generalized, the rash remained remarkably limited to the exposed parts (face, neck, arms and hands).

The authors were not able to identify the specific sensitizer, though the almost constant first involvement of the eyelids suggested an airborne irritant, either as dust or spray. The high incidence of dermatitis suggested the possibility of an inherent skin-sensitivity to morphine hydrochloride, but patch-tests with a 1:100 dilution of this substance were performed on 103 other subjects and were all negative.

The detailed case-records are followed by an interesting account by the factory manager of the history of the manufacture of morphine salts, together with his own observations and those of his colleagues as to the occurrence of "the rash". It was apparently well established that skin and respiratory troubles were ever present among the workers during the 19th century. It has been found by trial and error, during more than a century, that immunity is not acquired, and that it is useless to attempt to employ the affected worker again on the manufacture of opiates. With regard to the causative agent, there is some supporting evidence that an impurity may be responsible. Finally, the writer points out that "rash" of the type met with in manufacture does not occur as a result of morphine injection, for instance in the institutional treatment of morphinomania.

Photogenic Lesions

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PHYTO-PHOTO-DERMATITIS

by R. Klaber, *British Journal of Dermatology and Syphilis*, 54, 193-211, July 1942

The skin of sheep and cattle becomes sensitized to sunlight after feeding on certain plants. Photosensitization in man can result from taking certain drugs, notably sulphonamides. There is as yet no reliable evidence of human sensitization resulting from the consumption of any plant. External contact, however, with certain plants or plant extracts may lead to photosensitivity. The resulting reactions have certain special characters, which are distinct from those of a simple solar dermatitis and from all other eruptions which may be excited by sunlight. The special features are the latent period (24-48 hours) following exposure, and the subsequent rapid development of bullae, the subsidence of which is followed by pigmentation persisting for months or years. Several clinical variants described under different titles are now recognized as the result of this reaction. The use of some generic term to cover all these eruptions is clearly desirable, and Klaber has suggested the use of the term phyto-photo-dermatitis.

Stowers (1897) described the first case of this character before the London Dermatological Society. A bullous eruption had followed contact with wild parsnips. Forty years elapsed before Hirschberger & Fuchs (1936) in Germany and McKinlay (1938) in Great Britain described similar cases amongst troops on manoeuvres. The large bullae had raised the suspicion of contact with mustard gas! Jensen & Hansen (1939), working at the Finsen Institute in Copenhagen, showed that the eruption resulted from a photosensitization and identified the most active spectral range between 3,200 and 3,600 Å units.

Dermatitis bullosa pratensis striata of Oppenheim (Oppenheim & Fessler, 1928) is a bizarre eruption, all the features of which can be reproduced by exposure to sunlight after rubbing the skin with wild (or cultivated) parsnip flowers. There are, however, good reasons for supposing that this form of photosensitization can result from contact with other wild plants, not yet identified. Bullous eruptions have also been observed following contact with other members of the family Umbelliferae, e.g. cow parsnip, parsley, celery, angelica and carrots. In these cases, the possible role of photosensitization must be suspected although not yet proven.

Another botanical family, the Rutaceae, includes several species of plants which have been shown to be photosensitizers. Thus, the common rue (*Ruta graveolens*) and two

species of *Dictamnus* will produce bullae after subsequent exposure of the skin to sunlight. The same family includes all the citrus fruits. Of these, the essential oil from two varieties of lime (West Indian Persian) and that of bergamot (bergamot dermatitis) have been shown to produce photosensitization.

It has long been known that contact with figs may result in inflammation of the skin, followed by persistent pigmentation. Behcet, Ottenstein, Lion & Dessauer (1939) have shown that in these cases photosensitization is an important, though probably not an essential feature.

Klaber, after describing some personal cases and experiments, discusses the nature of the reactions involved, and the directions in which further research is required.

The effective spectral wave-lengths in all cases so far investigated appear to lie in the neighbourhood of the longer ultra-violet bands. These have been accurately determined only in the case of the parsnip and the fig. The definition of the effective wave-lengths in every case is desirable, since from the Grotthus-Draper law, there should be some coincidence between these and the absorption spectrum of the sensitizing substance.

Kuske (1938) had provoked photosensitization by the application of certain furo-coumarins—complex ketonic bodies obtained from bergamot and the roots of the masterwort (*Peucedanum ostruthium*, a member of the Umbelliferae). There have so far been no reports on the absorption spectra of these nor any other suspected substances.

Their entry into the malpighian layer is probably as necessary as Guillaume (1927) showed, was the case for certain dyestuffs to produce local photosensitization. This was made possible only by scarification of the horny layer of the skin. Thus, the possible necessity of friction, as well as a sufficient intensity of sunlight, under natural conditions, may suffice to explain the relative rarity of this group of eruptions.

There is abundant evidence for the view that these phenomena are not the result of idiosyncrasy or allergy. They can probably occur in any skin in which the necessary conditions are fulfilled.

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A CASE OF LIGHT SENSITIZATION

by D. Erskine, *British Journal of Dermatology and Syphilis*, 56, 195-198, September-October 1944

An electric welder, male aged 18, developed a sensitivity to light 2 months after starting this occupation and while receiving his first course of treatment for a primary syphilitic infection. He had suffered with eczema as a child. He developed erythema on the 9th day of anti-syphilitic treatment. The light-sensitivity was first apparent at the end of his first course of treatment with neoarsphenamine and bismuth, and appeared as a papular rash on the exposed parts of the body, there was also a sparse pustular-necrotic eruption on the trunk. Investigation showed the sensitivity to be a reaction to rays of relatively short wave-length, it therefore appeared to be associated with ultra-violet radiation, which is a more limited sensitization than that usually found in the more common type of adult light-sensitivity. Window-glass usually gave protection, so that while the patient was in the ward his condition improved, but he relapsed on going into the open air again. Blue violet, which allows many of the ultra-violet rays to pass, gave only partial protection.

Numerous attempts at desensitization were made. Minimal exposures of small areas of skin to distant mercury-vapour light were repeated daily on different parts of the body, but only a slightly increased toleration was achieved with six months' treatment. In addition, charcoal, creosote capsules, magnesium oxide and calomel by mouth appeared to assist the improvement of various attacks, but no beneficial effect

was noted with autohaemotherapy, protein shock, autogenous vaccines or urinary proteose injections. Sulphonamide was administered for a super-added impetiginous infection on one occasion, and caused an acute exacerbation of the light-sensitivity. The case has so far been refractory to all methods that have been employed. Investigation of this case suggests that the condition may be of occupational origin and that the patient is sensitive to the ultra-violet wave-bands, and thereby differs from the hitherto recognized light-sensitization of adult type, in which there is sensitivity to rays of the wider band, including at least a proportion of those of longer wave-length.

Neoplastic Lesions

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TRAGEDY OF MALIGNANT MELANOMA

by M. C. Tod, *Lancet*, 2, 532-534, 21/10/44

This paper stresses the fact that the removal of a mole for cosmetic reasons may result in the tragedy of death from multiple metastases of a young patient who had been in perfect health.

Although malignant melanoma is not common, 74 such tumours have been seen at the Holt Radium Institute, Manchester, during the last 3 years. Cases treated between 1933 and 1942 include 34 patients who died as a result of incorrect treatment. Incorrect methods used were (i) simple excision under local anaesthesia, (ii) ligature tied round by doctor, (iii) cautery with CO₂ snow, silver nitrate, etc. Any lesion of the skin which is pigmented, any history that a mole was present, at the site of an ulcerated lesion, or that a mole has been excised, must be regarded with the greatest suspicion. Six cases are described, in all of which malignant melanoma developed after excision of small moles for trivial reasons.

It is never justifiable to remove, for cosmetic reasons, a pigmented lesion which shows no signs of active growth. If the patient insists, the operation must be as radical as if there were signs of active growth in the lesion. If a lesion that is likely to be a melanoma is growing, treatment must be radical. Surgery must aim at excising a very wide margin of tissue all round the melanoma. Skin-grafting is often necessary to repair a wide gap. If radiotherapy is preferred either radium or x rays may be used. If the regional lymph-glands are involved, both primary and glands are widely excised with, if possible, the lymphatics between. Lymph glands should not be treated by irradiation except for palliation when they are completely inoperable. When metastases are already present beyond the regional lymph-glands, cure is practically impossible. Palliative irradiation is all that can be tried.

Many of the cases healed at the Holt Radium Institute are too recent to give survival-rates. But 73% of those whose primary treatment was radical are still alive, and only 28% of those whose first treatment was incomplete. The author emphasizes that melanoma, the common mole, is in the great majority of cases completely benign, and if left alone will remain benign. These percentages represent, therefore, a proportion of avoidable deaths, which were the result of ill-judged intervention.

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X-RAY TREATMENT OF MALIGNANT DISEASE OF THE SKIN

by B. W. Windeyer, *British Journal of Dermatology and Syphilis*, 55, 113-120, May 1943

In the treatment of the common malignant diseases of the skin—basal-celled and squamous-celled carcinoma—the use of x rays has to some extent fallen into disfavour and various forms of radium applications have been preferred on the grounds of a supposed superiority in both curative and cosmetic results. With modern x-ray machinery and adequate technique very similar results are obtained, and in the majority of these lesions the choice between x rays and radium depends upon the facilities available rather than on any specific response to the one or the other.

X-ray treatment fell into disfavour for several reasons, which the author now refutes as follows:

(i) *Inconvenient apparatus with inconstant output* With modern shock-proofed x-ray apparatus it is possible to apply and maintain the tube accurately in apposition, and to obtain a high dosage-rate by reduction in focal skin-distance. The output from such apparatus is remarkably constant.

(ii) *Inaccuracy of methods of dosage measurement* The adoption of the roentgen unit has resulted in standardization of dosage.

(iii) *Inadequacy of technique* Repeated small doses may cause radio-resistance and should not be used.

In all cases irradiations, whether by x rays or radium, should be planned as a single course of treatment, either as a single application or fractionated over a period not exceeding 30 days. For superficial lesions a beam produced at low kilovoltage with small percentage depth dose is most appropriate, but for some which are more infiltrating a greater percentage depth dose and therefore higher kilovoltage, is necessary. In the former the specially constructed "contact" therapy tube is particularly convenient, but if this is not available the ordinary shock-proofed tube used in dermatological practice makes an efficient substitute.

At the Middlesex Hospital a Philips tube working at 95 kV with short tubular brass applicators making a focal skin distance of 8 cm has been used. The resultant beam is very similar as regards quantity and quality to that of the Chaoul apparatus. For more infiltrating lesions 200 kV apparatus has been used with similar short tubular applicators and a focal skin distance of 26 cm.

Since 1938 cases of basal- and squamous-celled carcinoma of the skin at the Middlesex Hospital have been treated either with the 95 kV or the 200 kV x-ray apparatus. In the majority of small lesions a single application of 2,500 to 3,000 roentgens was given, but in extensive and infiltrating lesions the dose of 3,000 to 4,200 roentgens was fractionated and spread over 6 to 9 daily applications.

From 1938 to 1941, 165 cases of basal-celled carcinoma were treated, of whom 162 remain symptom-free. Thirty-five cases of squamous-celled carcinoma were treated. Twenty-one of them remain symptom-free and of the remainder the primary lesion has remained healed in 3 who have developed glandular metastases.

It is possible that recurrence may develop in some of these cases, but it is not likely to do so in any appreciable proportion as the areas treated are soft and free from induration. The cosmetic results are as good as those obtained in previous years by radium application.

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MULTIPLE SUPERFICIAL CARCINOMATA OF THE SKIN

by M. Johnson, *British Journal of Dermatology and Syphilis*, 57, 58-65, March-April 1945

The literature dealing with superficial carcinomata has, within the last 31 years, revealed great diversity in clinical and histological findings.

Bowen (1912) realized that his two cases differed clinically from, but presented the same histological picture as, some cases of Paget's disease of the nipple, x-ray dermatitis, and senile and arsenical keratoses and other conditions mentioned. There has been frequent confirmation of these findings, with the result that cases have been reported as "Bowen's disease", the "Bowen type of epithelioma", and "multiple basal-cell carcinomata of the Bowen type" merely because the histological picture has been similar to that described by Bowen. This has confused the conception of "Bowen's disease", and it is suggested that the term, if used at all, should include only those cases which correspond clinically and histologically with Bowen's original description.

Bowen did not classify his cases as a separate disease, but regarded them as belonging to the precancerous dermatoses, and wrote "In just which category they should be placed is not so clear."

Savataud (1931) suggests that Bowen's disease is malignant from the beginning, the earliest lesion being an intra-epidermal carcinoma, and he shows that all skin carcinomata, whether of basal, squamous or mixed type, commence intra-epidermally.

Becker & Obermayer (1940) still include Bowen's disease in the class of premalignant lesions, but point out that it is the histological picture which is characteristic and not the clinical entity

The author describes in detail the lesions found in a spinster of 54 years I-IV were confined to the trunk, and V-VI to the face and limbs

- I Multiple benign seborrhoeic warts
- II Multiple senile keratomata, showing in the lesions examined the histological picture of Bowen's disease Both types of lesion had been present for many years, but had increased in number for 6-10 years previously
- III Seventy-one erythematoid benign epitheliomata of Graham Little (1923), of 34 years' duration commencing when the patient was 20 years old
- IV One ulcerating basal-cell carcinoma of 6 years' duration
- V Psoriasiform carcinomata, of 1-4 years' duration and showing histologically an intra-epidermal carcinoma with spindle-cell proliferation similar to the third variety described by Savatard (1935) Similar lesions had disappeared spontaneously without scarring
- VI One cutaneous horn on the dorsum of the left foot, of 4 years' duration

There was no squamous-cell proliferation in the senile keratomata examined, but all showed histological evidence of malignancy in agreement with Savatard's findings (1931)

Four cases are more briefly described

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Nutritional Lesions

761

VITAMIN A AND THE SKIN

by H S Stannus, *Proceedings of the Royal Society of Medicine*, 38, 337-342, May 1945

In the course of nutritional surveys in Great Britain in which the author participated during the recent war, it became apparent that the follicular keratosis, which had come to be regarded as a criterion of vitamin-A deficiency (following observations made chiefly among native inhabitants of the Far East), was the same as keratosis pilaris, but had not been recognized as such by medical men interested in nutrition but untrained in dermatology

The author describes the condition as seen in a review of 8,000-9,000 persons, of whom more than half were children of school age He then reviews the evidence which led to the belief that "follicular keratosis" was due to vitamin-A deficiency, referring to a number of descriptions of cases in China, East Africa, Ceylon, India and Malaya, and reaches the following conclusions

That "follicular keratosis, phrynodema, etc," appears to be identical with keratosis pilaris, that the actual pathogeny of the condition remains uncertain, that it seems questionable whether a vitamin-A deficiency should be looked upon as a specific cause, though under certain circumstances it may be a factor in causation together with a lack of other essential food-factors, and metabolic disturbance of a pre-disposed skin, due to cold or trauma

In the discussion which followed, a speaker pointed out that this question could not be settled without vitamin-A estimations in cases of keratosis pilaris

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DARK-ADAPTATION STUDIES IN PATIENTS WITH DISEASES OF THE SKIN

by A Porter & H J Rogers, *British Medical Journal*, 1, 840-841, 16/6/45

As a measure of vitamin-A nutrition, the authors carried out dark-adaptation estimations in a group of about 100 cases of a wide variety of skin diseases, from the out-patient department of St. John's Skin Hospital, and a control group,

of about the same size, of friends of patients attending another hospital Subjects under 16 and over 45, those with various ocular diseases or a history of general disease conditions, and pregnant and nursing mothers were excluded

Method Subjects were put into the dark room at 10-minute intervals, after being in the hospital not less than half an hour to guard against the effects of exposure to previous high brightnesses The first subject was tested at the end of 30 minutes, followed by the remainder at 10-minute intervals The test-object was first shown at a brightness which could be seen fairly easily, this being decreased until the threshold reading was obtained The test was then continued to 40 minutes Subjects showing a greater difference between the readings at 30 and 40 minutes' dark-adaptation time than was expected were re-tested The threshold measurements of brightness seen at 30 minutes dark-adaptation time were taken

There was no significant difference between the mean threshold measurements of brightness at 30 minutes' dark adaptation in the patients with skin disease and the control group

Lesions of Uncertain Aetiology

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ERYTHEMA NODOSUM — A SEVERE TYPE IN MIDDLE-AGED WOMEN

by E Frankel, *Lancet*, 1, 817-818, 30/6/45

It is now generally accepted that erythema nodosum is a non-specific inflammatory reaction of the skin to a variety of agents, including the tubercle bacillus and the streptococcus, and not a specific disease

The author reports on 19 cases of erythema nodosum in women, which were unusual in that the patients were all middle-aged, and the illness was more severe than usual, with longer fever and more pronounced toxæmia Involvement of the joints was conspicuous and the rash on the extensor surface of the legs was always very extensive and quite characteristic Recurrent attacks were frequent There was no family or past history of tuberculosis or rheumatism Clinical features were distinct in all cases, and all patients made a good recovery

Throat swabs were taken from all patients and from 9 haemolytic streptococci were grown These patients had streptococcal agglutination tests performed and 7 showed a high agglutination titre, varying from 1 5120 to 1 160 (normal up to 1 80) Blood cultures were sterile and meningococcal fixation tests and Wassermann reactions were negative The blood-sedimentation rates varied There was no radiological evidence of intrapulmonary disease

The clinical picture reported seems common and should be recognized The rash and the course of the disease are so typical that knowledge of it will help in diagnosis and prognosis In view of the haemolytic streptococcal infection of the throat and the high streptococcal agglutination titre in a number of the patients, sensitization of the skin by streptococcal toxin is the probable cause of the inflammatory reaction The severe constitutional disturbances preceding and accompanying the skin reaction must be due to toxæmia, probably also of streptococcal origin

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A CASE OF FOX-FORDYCE DISEASE

by A. C Roxburgh, *British Journal of Dermatology and Syphilis*, 55, 121-124, May 1943

The case described occurred in a woman aged 25 years, who had been married for 2½ years Irritation began in the axillae 3 weeks after marriage and extended to breasts, pubes, labia majora and lower abdomen Menstruation had always been prolonged and frequent, this did not change with the onset of irritation The irritation interfered with her work as a civil servant and was worst at night and particularly severe in axillae after coitus It had no relation to the menstrual cycle On examination, the lesions were closely-set, dome-shaped, follicular papules, dark brown in colour, in both axillae and extending downwards to the areolae of

the breasts, rather flattened papules on the areolae, dome-shaped papules on the pubes extending upwards to the umbilicus, also on the labia majora, but none about the anus. The axillary and central pubic hair had disappeared. The histology of three of the papules excised from $\frac{1}{2}$ inch [about 1.25 cm.] below the umbilicus was as follows: the epidermis and upper corium showed the usual changes characteristic of lichenification with a moderate round-cell infiltration, denser around the upper part of the hair follicles and sweat ducts. The apocrine glands underlying the papules appeared to be normal. The distribution of the eruption closely corresponded to that of the apocrine glands and even in areas where apocrine glands are not constantly present, viz just below the umbilicus, papules and apocrine glands were present together, each papule in the section having an apocrine gland beneath it. The appearances suggested that the secretion of the apocrine glands was irritating though the glands themselves were not inflamed. X rays (200 r) to the left axilla produced no benefit. Some relief was obtained from a lotion containing 12% of lotio plumbi (liquor plumbi subacetatis dilutus) and liq. ricis carbonis, but the treatment which did the most good was a daily dose of 1 mg. of stilboestrol. This produced immediately a great reduction in the symptoms and, after 3 months, in the size of the papules. Oestrin ointment [composition not given, but stated to be "5000 units per g."] applied to the irritating areas was ineffective.

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BLOOD CHOLESTEROL VALUES IN CASES OF GENERALIZED PRURITUS

by A. E. Somerford, *British Journal of Dermatology and Syphilis*, 55, 98-102, April 1943

In view of the fact that increased blood-sugar or blood-urea is found in only approximately 50% of cases of generalized pruritus, it was thought that an investigation of blood-cholesterol might be of interest. Forty-three patients (21 male and 22 female) with normal blood-sugar and blood-urea were examined. Their ages varied from 28 to 85, and 76% were over 50 years of age. Increases in blood-cholesterol were found in 20 patients, the results varying between 242 and 586 mg. per 100 cm³ of blood. Seventeen patients were normal and 6 showed decreases of from 158 to 100 mg. Patients with a definite skin lesion such as lichen, scabies, etc., or with infected scratch marks, or with generalized diseases such as jaundice or diabetes were not included in the investigation.

Generalized pruritus is usually a disability of later life and affects the sexes equally. It may be due to various causes, among which changes in the blood chemistry would appear to be one factor. These chemical changes probably act by direct irritation of the nerve-endings in the skin. The author suggests that altered cholesterol-levels in the blood may be a cause of pruritus.

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KERATODERMIA BLENORRHAGICA SOME FURTHER OBSERVATIONS AS TO AETIOLOGY

by A. G. Fergusson & F. J. Lees, *British Journal of Dermatology and Syphilis*, 55, 125-130, May 1943

The authors describe in some detail the history, clinical and bacteriological findings and progress of an apparently typical case of keratoderma blenorragica which is usually regarded as a cutaneous manifestation of gonococcal infection. In this case, however, a history and signs of present or previous gonorrhoea were entirely absent, although there were other findings characteristic of "metastatic" gonorrhoea, including interstital keratitis, multiple arthritis and endocarditis.

Attention has previously been drawn to the occurrence in gonorrhoea of urticarial and erythema multiforme-like rashes, which have sometimes merged imperceptibly into keratoderma blenorragica.

The authors conclude from this case and others published elsewhere that blenorragic keratoderma is probably a non-specific eruption aetologically and histologically allied to such disorders as urticaria, erythema nodosum and erythema multiforme, and that it should be classified not among the hypertrophies, as is usually the case, but among the exudative inflammatory diseases of the skin.

A CASE OF PSEUDOMEMBRANOUS INTERTRIGO

by Alice Carleton, *British Journal of Dermatology and Syphilis*, 55, 154-158, June 1943

The patient was a female infant aged 7 months, weighing 12½ pounds [about 5.67 kg]. Her birth-weight was 6½ pounds, she had been breast-fed for 4 months and her general health had always been good. Her father and elder sister were healthy. Her mother had undergone sanatorium treatment for pulmonary tuberculosis for 3 months of the pregnancy, but had since been symptom-free.

At the age of 5 weeks she developed external otitis of both ears and similar lesions later appeared in the natal cleft, vulva, right axilla and in the furrow between the chin and lower lip. All these areas showed sodden desquamation surrounded by a halo of bright erythema, except in the case of the axilla where the edge of the lesion was sharply defined.

The Wassermann and Kahn reactions were negative, the tuberculin patch-test was negative on two occasions. Faeces, urine, blood-count and blood sugar were all normal. The biopsy report was that the lesion resembled an intertrigo with hyperkeratosis and follicular keratosis. Bacteriological examination showed that streptococci, staphylococci, *Ps. pyocyanea*, diphtheroids, *B. coli* and *Pr. vulgaris* had been found on different occasions, but no single organism had been constantly found, and repeated search for *B. diphtheriae* and *Monilia* had been negative on every occasion.

Various treatments given with no permanent benefit included crystal-violet and brilliant-green paint 0.75%, penicillin locally, 5% sulphamidamide ointment, dettol cream, 2% tar ointment, 4% tannic acid in Alibour's lotion, halibut-liver oil by mouth and locally, quinalor ointment, sulphathiazole powder. X rays, 150 r with 1 mm. Al. filter, irritated the skin. Alum-precipitated toxoid, initial dose 0.2 cm³ produced no effect. Riboflavin and ascorbic acid, given in daily doses of 9 mg. and 50 mg. respectively, were also ineffective.

Differential diagnosis. Moniliasis may be associated with an intertrigo, but no mycelium and spores could be demonstrated in this case. There were no symptoms of lung, kidney or joint involvement, there was no buccal or nasal involvement and the child's general health remained good. Finally, there was no response to the usual treatment for moniliasis.

Anriboflavinosis was considered but against this there was absence of dryness or fissuring of the lips, of glossitis and of keratitis or circumcorneal injection.

Cutaneous diphtheria may present a clinical picture closely resembling the present case, but the pinna and axilla are not usually involved and the typical circumferential clear or milky vesicles seen in diphtheria were never observed, nor was *B. diphtheriae* found in the lesion. During 6 months' hospital life there was no transmission of infection.

This case suggests that a mixed infection with staphylococci, streptococci, *Ps. pyocyanea* and *Pr. vulgaris*, may bring about a pseudomembranous intertrigo, resistant to treatment and with a strong clinical resemblance to both clinical diphtheria and moniliasis.

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LYMPHADENOMA ITS AETIOLOGY, AND ITS SKIN-LESIONS

by E. C. Warner, *British Journal of Dermatology and Syphilis*, 56, 129-135, May-June 1944

There are two schools of thought concerning the aetiology of lymphadenoma, the one maintaining the inflammatory and the other the neoplastic hypothesis. It is essentially a disease of the reticulo-endothelial system, which usually first manifests itself in the lymph glands, but may subsequently involve any organ in the body, the patients usually dying of cachexia, as a result of multiple lesions.

Clinically, the inflammatory hypothesis seems probable. The disease may occur at any age, although most commonly between the ages of 20-40 years. In children it is particularly severe. The lymphoid tissue of the upper respiratory and intestinal tracts afford a portal of entry through which lymph glands may be affected. The family incidence is very small. The temperature chart suggests an infection. There is almost invariably a relative or an absolute rise in polymorphs (unless deep x rays have been used) when the

disease is established. Histologically, there is fine fibrosis in the affected glands, and acute cases show large numbers of polymorphs, but unlike malignant disease, the capsule is not invaded.

The bacteriological studies of Mervyn Gordon (1937) demonstrated great numbers of "elementary bodies" resembling a cocco-bacillus, in all the acute cases studied, an organism which he stained successfully with Loeffler's flagella stain. Controls from normal glands showed granules of larger dimensions than the "elementary bodies" and these mostly disappeared in 1% acetic acid, whereas the "elementary bodies" were unaffected. Comparison of these bodies with those of vaccinia showed them to be slightly larger but the comparison is very close.

Injection of an emulsion of "elementary bodies" into the brains of rabbits and guinea-pigs produces a characteristic encephalitis, although the significance of this finding has been questioned. Whatever interpretation is put on this intracerebral test, it is generally accepted that if a positive reaction is obtained with material from a lymph gland, the disease is lymphadenoma.

The author with Gordon (1937) was able to study the clinical effects of emulsions of the elementary bodies in patients with lymphadenoma. Doses of a sensitized vaccine prepared from human glands, even in dilutions of 1:40,000 to 1:100,000 produced in some patients with lymphadenoma, after 0.2 cm³

temperature reactions, further glandular swelling, and a generalized rash. Two patients in whom the main treatment was small doses of sensitized lymphadenoma vaccine are alive and well with no enlarged glands or other pathological signs 15 years and 8 years after starting the vaccine and without any treatment for a period of 7 and 6 years respectively. In other cases, clear results could not be obtained. The method of preparation of the sensitized vaccine is long and tedious, and an autogenous vaccine, although preferable, could not be prepared for each case.

Of the skin lesions of this disease, pruritus usually starts on the front of the legs or the dorsum of the feet and can be most distressing. Herpes zoster occurs in approximately 30% of the cases. Papular eruptions of the trunk may occur and there may be skin ulceration usually in suprasternal and axillary areas, or in the upper part of the neck.

The author suggests that lymphadenoma stands in an intermediate position between the granulomata and the neoplasms and refers to the work of Rous, Ledingham, Gye, Russell-Amies, Andrewes, and others who have shown that there is a sarcoma-exciting agent in animals and birds, which exists in the form of "elementary bodies" and that those so infected show an agglutination to these "elementary bodies" in their blood serum.

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THE TREATMENT OF PLANTAR WARTS BY FORMALIN

by S. Thomson, *British Journal of Dermatology and Syphilis*, 55, 267-269, November 1943.

The value of this treatment was discovered accidentally. A woman of 56 with plantar warts was supplied with a 3% aqueous solution of formalin, to dab on the warts, during a 3-weeks delay until it could be arranged for her to have x-ray treatment. When she returned to the hospital at the end of the 3 weeks, the warts had entirely disappeared, leaving punched-out holes with no traces of wart-formation.

Subsequently 36-40 cases of warts were treated with formalin lotion. The majority of the patients were children of school age. It was found that the treatment was best restricted to the palms and soles. Elsewhere, the degree of eczematization that ensued was disproportionate to the value of the treatment. Of the whole series, all but 6 were kept under observation for 2-3 months after the lesions had cleared. Treatment failed in 2 cases only.

A 3% aqueous solution of formalin was used, some being poured into a small saucer in order that either the heel or the anterior portion of the sole of the foot could rest in the solution, without its reaching the thinner skin on top of the foot. The patients were instructed to soak the area for 10 minutes

each night in this way. In most cases the pain disappeared in 7-10 days and, at the end of 3 weeks, the warts showed as white macerated plugs, which could easily be scraped away, leaving soft epithelium in the depth of the crater. A few cases did not undergo these changes until after 7-8 weeks. With this treatment, the author solved the problem of an outbreak of warts in a girls' school.

Dermatophytosis

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THE PHENOL-CAMPHOR TREATMENT OF DERMATOPHYTOSIS

by B. Phillips, *British Journal of Dermatology and Syphilis*, 56, 219-227, November-December 1944.

The author reports the results of an investigation into the phenol-camphor treatment of tinea pedis, tinea cruris and tinea axillaris, members of the group of superficial fungus diseases known as dermatophytosis. This treatment was first introduced by Francis (1941) who reported that he had successfully treated tinea pedis with a combination of equal parts of phenol and camphor.

For purposes of the investigation, 3,250 soldiers, and 500 women of the Auxiliary Territorial Service, were examined. The incidence of dermatophytosis was as follows:

a. Of 3,250 men examined, 5.5% were found to be suffering from dermatophytosis.

b. Of 500 women examined for tinea pedis alone, 6% were affected.

The total number of cases of dermatophytosis used for the experiment was 230, composed of

137 cases of tinea pedis
83 cases of tinea cruris
10 cases of tinea axillaris

The diagnosis of every case was made on clinical grounds, and confirmed by microscopy.

Phenol-camphor was prepared by placing equal quantities of pure phenol and pure camphor in a mortar and triturating with a pestle until liquefaction occurred. The solution was then ready for use. Ung. acid. benz. co. B.P.C. (Whitfield's ointment) with the addition of 0.5% dithranol ("derobin") was used as the control.

As the lesions of these forms of dermatophytosis are approximately symmetrical, it was decided to use the phenol-camphor on the left side, and the control on the right side of the body in every case, irrespective of clinical differences. The phenol-camphor was painted on to the lesions four times daily until cure was established, and the control was used twice daily until erythema occurred, and the areas were then soothed by the application of calamine lotion.

The average times for cure were

Tinea cruris	4.3 days
Tinea pedis	4.5 days
Tinea axillaris	4.9 days

There were no failures in 230 cases treated. Only 1.7% of cases were noted to have relapsed in a three months follow up period.

In spite of warnings (Calvery, 1942, *Journal of the American Medical Association*, 1942, *Lancet*, 1942) regarding the supposed toxicity of the phenol-camphor preparation, there were no cases with either local or general reactions. In the latter two-thirds of the experiment, all cases were treated as out-patients and performed their normal duties.

Phenol-camphor had the following advantages over other forms of treatment, for example, the control (Whitfield's ointment with 0.5% dithranol). It was non-greasy, easily applied, non-irritating, and non-staining. No dressings were required. Infected areas were not obscured (by staining or erythema), and the end-point of treatment was easily recognized. It could be used until a cure was effected, and the medicament did not need to be changed during the course of treatment.

The author regards phenol-camphor as an innocuous medicament, and a specific remedy for these forms of dermatophytosis

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Ointment Bases

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A METHOD OF TESTING ABSORPTION FROM VARIOUS OINTMENT BASES

by J Rae, *British Journal of Dermatology and Syphilis*, 56, 92-94, March-April 1944

Advantage was taken of the fact that crystalloids in solution will pass through a cellulose transparent film into distilled

water, and the various results obtained probably represent the action of an ointment when applied to the broken skin

The crystalloid used was sodium chloride in a concentration of 2%. One end of a glass tube, 10 cm long and 2.5 cm diameter, was closed by means of a piece of non-moisture-proof cellulose film drawn well up the outside and secured with a rubber band. Twenty-five g of the ointment was introduced into the tube and gently pressed down against the cellulose. Fifty ml of distilled water was placed in a small beaker, and the tube, suitably supported, placed in it so that the end covered with the cellulose was immersed to a depth of about $\frac{1}{2}$ -inch (about 1.3 cm). This was left for 24 hours for diffusion to take place, the solution in the beaker being then titrated with N/10 silver nitrate.

In all, 20 bases were tested and the number of ml of N/10 silver nitrate required was found to vary with the type of base tested, ranging from 0.1 ml for lard to 23.8 ml. for pectin (100 grade) 5% in distilled water. This latter base plus lanette wax SX 10% gave a figure of 19.0 ml. Methyl cellulose 10% in distilled water required 14.9 ml.

The results obtained show very clearly the advantage of the newer type of non-greasy ointment base.

REPORT

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A HUMAN EXPERIMENT ON THE RELATIONSHIP OF YAWS AND SYPHILIS

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To what extent the immunity conferred by yaws protects against syphilis and vice versa is a question of considerable interest, and one which has not been clearly elucidated by animal investigations.

An experiment in which an individual recently suffering from active tertiary yaws (framboesia) was infected experimentally with syphilis is here recorded.

Akwa N., aged 18 years, whose occupation was alternately bar-tender and bird-snarer, was first seen at the end of 1942, when he presented himself with multiple serpiginous ulcers on the dorsum of the right foot and the lower third of the anterior aspect of the right leg. The ulcers, which were of 2 years' duration, were shallow, with a slight sero-sanguinous discharge. Smears from them yielded staphylococci only. The appearance of the lesions was typical of yaws.

His previous history was as follows. At the age of 6 he had an attack of yaws, a fact corroborated by his mother, and the lesions were treated with native medicine. At the age of 8, when cooking yams, the pot boiled over and caused extensive burns on the legs and left elbow which, he states, took 2 years to heal. On examination he was found to have positive Kahn and Ide reactions. He also had perioritis of both tibiae and areas of depigmentation on the skin of the legs. He was given eight intravenous injections of neoarsphenamine, a total of 3.6 g., and the ulcers rapidly healed. His Kahn and Ide reactions, however, remained constantly positive. He denied having had a penile sore at any time. The inguinal lymph-nodes were small and painless.

On May 4, 1945, with his full consent, he was inoculated with serum from the chancre of a case of primary syphilis. The serum showed *Treponema pallidum* in large numbers by dark-ground examination. He was injected on two places (i) at the dorsum of the penis and (ii) on the abdominal wall about 2.5 cm. below the umbilicus. A singular linear scratch was made.

7.5.45 No reaction in either area.

18.5.45 No reaction on the abdomen, but a small linear sore was apparent on the scratch on the penis. Dark-ground examination of a drop of exudate from this sore was negative.

21.5.45 The sore had enlarged and become circular, while the inguinal lymph-nodes of both sides were enlarged and slightly tender. Dark-ground examination was still negative.

25.5.45 The penile sore had now enlarged and was nearly 1 inch [2.54 cm.] in diameter, it was slightly softer than before.

Trep. pallidum were now seen by dark-ground examination, and again 2 days later. The inguinal glands were still tender, but had no tendency to form a bubo.

27.5.45 While the penile sore remained the same, a circular indurated sore had now appeared at the point of inoculation on the abdominal wall. This had all the appearances of a primary chancre, but *Trep. pallidum* could not be demonstrated in it by dark field.

2.6.45 A course of neoarsphenamine with bismuth was begun, and after the second injection healing of both sores took place rapidly.

In order to demonstrate that the sores did not result simply from scarification in a patient with yaws, an exactly similar scarification was made on the lateral side of the abdominal wall, a drop of physiological saline being placed on the scarified area. No sore resulted.

It would thus seem that this patient, though possessing positive serological reactions due to yaws infection which was not active at the time, was capable of being infected with the spirochaete of syphilis, as shown by the occurrence after the usual incubation period of a primary chancre with enlargement of the inguinal lymph-nodes.

(Received 13/9/45)

BOOKS

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149

576 8 (02)

151

61 (061)

A TEXTBOOK OF BACTERIOLOGY

by R W Fairbrother Fourth edition (third impression) London, William Heinemann (Medical Books) Ltd, 1945 463 pages, 6 plates, 12 figures 22 x 14 cm 17s 6d [£0 875]

The record of Fairbrother's *Textbook of bacteriology* since its publication testifies to its popularity. Four editions have appeared in the last eight years, and this is the third reprint of the fourth edition.

The first part of the book starts with the story of the early bacteriologists and their discoveries, and goes on to give a clear elementary account of such subjects as the morphology and biology of bacteria and their cultivation, together with chapters which describe the fundamental principles of immunity. Other chapters are devoted to the classification of bacteria and their relation to medicine, the latter including a useful summary of the methods employed in the identification of bacteria. To the fourth edition has been added a chapter on chemotherapy which deals with the pharmacology and mode of action of the sulphonamides, together with a short note on penicillin.

The second section is devoted to systematic bacteriology and is an account, short but entirely adequate for the needs of the undergraduate student, of those bacteria with which he is expected to be familiar. Noteworthy in this section is the attention paid to the biological relationship of allied genera and species. This mode of treatment permits a more connected account of the various bacteria than appears in those elementary text-books which limit themselves too rigidly to the purely medical applications of bacteriology. This section also includes chapters on the spirochaetes, Rickettsiae, filterable viruses, bacteriophage and the bacteriology of water and milk.

The third part, describing the use of the microscope, staining methods, the preparation of culture media and serological technique, is a short one of some 26 pages, in accordance with the author's expressed intention not to overload the book with masses of technical detail.

Necessarily dogmatic, as a book of this size must be, it yet does not fail to indicate those points at which our present knowledge consists of only tentative conclusions, and to the student, undergraduate or postgraduate, who is looking for a reliable account of modern bacteriology in concise form, the work can be confidently recommended.

150

576 809.3

HANDBOOK OF PRACTICAL BACTERIOLOGY

by T J Mackie & J E. McCartney Seventh edition Edinburgh, E & S Livingstone, Ltd, 1945 720 pages 19 x 13 cm 17s 6d [£0 875]

The latest edition (the 7th in 10 years) of this book is divided, as in previous editions, into three sections. The first is a short account of such elementary principles of the biology of micro-organisms and of immunology as are necessary for the understanding of the practical bacteriology that follows, the second deals with bacteriological technique and contains detailed accounts of all the usual laboratory procedures. The third section gives concise descriptions of the micro-organisms of importance to the clinical bacteriologist, with particular emphasis on the methods of bacteriological diagnosis in the various infections, and includes chapters on the pathogenic protozoa, pathogenic fungi, Rickettsiae and viruses. In addition, an appendix introduced into the previous edition "for the inclusion of new contributions to bacteriological knowledge and technique which had assumed special importance after the text had already been revised", has been expanded. It now forms a useful résumé of recent advances in practical bacteriology which may spare the reader more than one search through the journals of the past five years or so, while the references given will help him if he wishes to pursue the subjects further. A few of the items included are: antibiotic substances of fungi and bacteria with special reference to penicillin, testing of sensitivity of bacteria to sulphonamide compounds and to penicillin, titration of bacteriostatic action of blood during penicillin treatment, fluorescence microscopy, desoxycholate-citrate-agar, bacteriological examination of air and air disinfection, bacteriological examination of infected wounds, with special reference to infection by sporing anaerobes.

For the undergraduate student who is approaching the subject for the first time the book is probably too specialized in scope, but the senior student who wishes to revise his bacteriological knowledge and to see it afresh from the clinical angle will find it of considerable value, particularly part 3. The main purpose of the volume, however, is still to provide a practical "handybook" for the laboratory worker, and in this purpose it again admirably succeeds.

LISTER INSTITUTE OF PREVENTIVE MEDICINE

Report of the Governing Body, 1945

published by the Lister Institute, Chelsea Bridge Road, London, S W 1 1945 14 pages 27 x 21 cm

For a review of the report for 1944 see *BMB* 606/107

The report of the Lister Institute for the year 1945 was presented by the Chairman of the Governing Body, Sir Henry Dale, at the annual meeting on June 18.

Some members of the staff are still dispersed on various forms of war service.

The *Medical Research Council* is continuing its unit for research into, and filtration of, blood plasma and serum for transfusion.

Bacteriological, immunological and pathological studies Dr A. Felix has continued work on the typing of typhoid, paratyphoid and food-poisoning bacilli with the Vi bacteriophage. One further Vi-phage type of typhoid bacillus has been identified. Further progress has been made with the typing of *Bact. typhi-murium*, one of the most common causes of food poisoning, but the practical value of the bacteriophage typing of this organism is not as great as that of the typing of typhoid and paratyphoid B bacilli, as strains of *Bact. typhi-murium* are often found to be devoid of the Vi antigen.

Following observations by Dr Felix, the Emergency Public Health Laboratory Service, in co-operation with the Ministry of Health, the Department of Health for Scotland and the three fighting services, has now prepared a scheme for the routine application of the Vi-agglutination test to future cases of typhoid fever. It is hoped thus to differentiate between chronic carriers of typhoid bacilli and temporary excretors, and to keep a check on the former.

Work has been carried out on dysentery prophylaxis, gas gangrene (including research to improve the quality of the antigens used for immunizing horses), hyaluronidase production, whooping cough, the nuclear structures in bacteria, cardiac hypertrophy, and trichomoniasis in cattle.

Vaccinia virus studies Dr D. McClean has continued his work on the cultivation of vaccinia virus, and has also carried out investigations on the antigenicity of the virus inactivated with alcohol, on the virus-neutralizing activity of serum from recently vaccinated persons, and on the storage of vaccine lymph dried from the frozen state.

Biochemical studies *Specific blood-group substances* Dr W. T. J. Morgan and Miss M. R. B. Waddell have examined the chemical properties of the products of acid hydrolysis of the A-substances derived from hog gastric mucin and pseudomucinous ovarian cyst fluids; they have isolated the B-substance from ovarian cyst fluid and converted it into a full antigen.

Dr Morgan and Dr D. B. Steabben have continued their experiments designed to suppress and control the natural anti-A agglutinin and have investigated more particularly the effect of the injection of A-hapten into rabbits whose serum shows a high anti-A agglutinin titre. Similar experiments in man have been carried out in collaboration with Dr J. F. Loutit.

Dr R. L. M. Syngé has continued his studies on gramicidin, on the interaction of pairs of the three antibacterial agents, gramicidin, "gramicidin S" and penicillin, and on amino-acid analysis.

Biophysical and physio-chemical studies New methods have been developed for the separation of fibrinogen and prothrombin from human plasma. Work has been carried out on the development of a tray type freeze-drier, which has been tested by a study of the drying of calcium penicillin, human plasma and human milk. An apparatus has also been constructed for the freeze-drying of vaccine lymph, human milk and human plasma products. Investigations have also been made in foetal and maternal haemoglobin.

Endocrinology Dr V. Korenchevsky has continued his studies on the effects of different combinations of hormones and vitamins on adult and old rats.

Nutritional studies Dr H. Chick and Mr E. B. Slack have continued work on the growth-promoting value of the nitrogenous substances in potato and wheat, and have also investigated the supplementary action between these and nitrogenous materials in yeast and an aqueous beef extract.

The human experiment on deprivation of vitamin A, which was begun, under Miss E. M. M. Hume, in July 1942, was concluded in September, 1944. Miss Hume has collected the available data and is preparing it for publication. An experiment on the same subjects on deprivation of vitamin C has been begun.

Miss Hume and Miss Henderson Smith have made various studies on vitamin A deficiency. Biological estimations of vitamins have been carried out by various workers.

Dr Dagmar C. Wilson, in collaboration with other workers, has continued her work on the incidence of endemic goitre in relation to the iodine, fluorine and calcium content of drinking water and has also investigated the incidence of congenital deaf-mutism in relation to low iodine-content of drinking water.

Other work includes studies by Dr P. Ellinger and Mr Benesch on nicotinamide and related compounds. Researches on the

solation of a 2,3-diketogulononic acid, on Lugg's method for the determination of vitamin C, and on practical problems for the fighting services have been carried out by Dr S S Silva and his 20-workers of the external scientific staff of the Medical Research Council

National Collection of Type Cultures Over 4,500 cultures have been distributed during the year—a substantial increase on the previous year—and some 200 strains were lodged for maintenance or investigation

152 611 (02)
A COMPANION TO MANUALS OF PRACTICAL ANATOMY

by E. B. Jamieson Sixth edition London, Oxford University Press, 1945 736 pages. 16 × 10 cm 16s. [£0 8]

This book is designed to provide a concise account of the naked eye anatomy of the human body. It was first published in 1911 and has since then become accepted as one of the best pocket reference books on the subject. While it does not attempt to take the place of the larger text-books of anatomy, it does contain a vast amount of information in a small compass, and is invaluable for revision purposes

This edition follows closely the general arrangement of its predecessors and no material changes in content have been made. The terminology used is the Birmingham revision of the Basle anatomical nomenclature. The structures are described systematically, but the more crowded regions are described topographically also

153 612 111 11
HAEMOGLOBIN LEVELS IN GREAT BRITAIN IN 1943

(With Observations upon Serum Protein Levels)

by the Committee on Haemoglobin Surveys. Medical Research Council Special Report Series, No 252. London, H.M. Stationery Office, 1945. 128 pages. 25 × 15 cm. 2s. [£0 1]

Discussions between the Ministry of Health and the Medical Research Council, prompted by a desire to obtain some evidence as to the nutritional state of the British people in the fourth year of war, resulted in the appointment by the Council of a special committee to co-ordinate surveys of the haemoglobin and serum-protein contents of the blood in representative samples of the population, with special reference to nutritional and other circumstances of war-time. Details of two such surveys form the greater part of this report, one dealing with the haemoglobin levels of large groups of the general population, and a second dealing on a smaller scale with serum-protein-levels among adults. To secure the uniformity of technique necessary for the results of such a survey to be mutually comparable, calibrated apparatus and standardized procedures were used. The Haldane modification of Gowers's method of haemoglobinometry was selected and all observers were subjected to an accuracy test, personal variations being taken into consideration in interpreting the results obtained in the survey. The absence of satisfactory indices of normality for subjects of different ages, civil states, stages of pregnancy, etc., and of satisfactory pre-war base-line data for the different social and occupational groups made it more difficult to assess the trend of the haemoglobin level during the war. Nevertheless, the experiences recorded in this report will undoubtedly be of great value to future workers in this and allied fields of nutritional research. From the evidence afforded by these investigations, the committee have concluded that the general situation in the fourth year of war was reasonably good, but that an effort is needed to improve the haemoglobin levels of young children, pregnant women, and the poorer members of the population

154 612.392
NUTRITIVE VALUES OF WAR-TIME FOODS

(Tables compiled for the Accessory Food Factors Committee)

Medical Research Council War Memorandum No 14 London, H.M. Stationery Office, 1945 59 pages. 25 × 15 cm. 1s [£0 05]

Data resulting from the work of numerous institutions and Government departments have been used in the compilation of the food tables contained in this memorandum, which have been prepared mainly for three reasons (i) values for the composition of many foodstuffs consumed in war-time were not available in existing tables and the differences between the values for war-time and peace-time foods are often great (ii) in Britain, values for the vitamins in foods have not previously been scrutinized and tabulated in a form suitable for use in evaluating dietary data, (iii) dietary surveys of the population, which are being carried out by the Ministry of Food and the Ministry of Health, have created a demand for food tables giving, for raw foods, values for the proteins, fats and carbohydrates, and for the relatively small number of minerals and vitamins most likely to be deficient in human diet

The Introduction to the tables gives an account of the material used, and an explanation of methods of calculating values and of the meanings of the terms "as purchased" and "edible portion" as used in relation to the foods listed. Table I sets out the composition of the "edible portion" of foods per 100 g., with an appendix of vitamin-D and riboflavin values per 100 g. "edible portion." Table II the composition of foods "as purchased" per 100 g. and Table III the composition of foods "as purchased" per ounce (about 28 g.) These tables, which cover a wide range

of foods, classified under the headings "Cereals and cereal products," "Meats, meat offals and meat products," "Fish—fresh, cured and canned," "Dairy products," "Fruits—fresh and canned—and nuts," "Vegetables—fresh and canned—and pulses," "Sugar, sweets and preserves," "Food concentrates," and "Beers," should prove most useful in evaluating dietary surveys and in planning human dietaries where a high degree of scientific accuracy is not required. They are unsuitable, however, for survey by the individual method or for use in exact experimental investigations

155 615.3
A TEXT-BOOK OF PHARMACOGNOSY

by G. E. Trease Fourth edition, revised with the assistance of H. E. Street & E. O'F. Walsh. London, Baillière, Tindall & Cox, 1945 799 pages, 270 illustrations & 9 maps. 22 × 14 cm £1 7s 6d [£1.375]

The author defines pharmacognosy as including the study of the history, commerce, cultivation, collection, preparation for market and storage, chemistry, identification and evaluation of crude drugs and other raw materials of vegetable and animal origin

This is a reliable textbook for the pharmacist and pharmaceutical student, but is of little direct relevance to the medical reader. Nevertheless, the physician who would be interested to know something of the steps through which drugs of vegetable origin have passed before they reach the pharmacy will find this book full of unfamiliar information, and it might therefore be regarded as a useful acquisition to a medical library

156 616 (02)
TEXTBOOK OF MEDICINE

by Various Authors Edited by J J Conybeare. Seventh edition Edinburgh, E. & S. Livingstone, Ltd, 1945 1164 pages, 21 illustrations. 22 × 14 cm £1 10s. [£1.5]

This is one of the most important of the shorter textbooks of medicine. It presents the essentials of the subject with conciseness and clarity, and is of particular value to the senior student, who will find it an excellent introduction to the more exhaustive texts

In this edition a new section on sulphonamides has been contributed by the editor W D W Brooks has rewritten much of the section on pulmonary tuberculosis, bronchiectasis, bronchial neoplasms and asthma, and has contributed an article on sarcoidosis. The articles on adherent pericardium and constrictive pericarditis, left ventricular failure, and effort syndrome have been completely rewritten. A new article on perianteritis nodosa has been included

Much of the section on renal diseases has been revised or rewritten by A. A. Osman and in the section dealing with neurology F. M. R. Walshe has rewritten the chapters on sinus thrombosis, acute and subacute myelitis, epilepsy, and the epidemiology of poliomyelitis. In the section on diseases of the skin, G. B. Dowling has added an article on lichen planus and has rewritten those on impetigo and eczema

The book is arranged under the following sectional headings (i) infectious diseases, (ii) tuberculosis, (iii) venereal diseases, (iv) tropical diseases, (v) diseases due to metazoan parasites, (vi) diseases of infants, (vii) diseases due to physical agents, (viii) poisonings, and intoxications, (ix) disorders of the endocrine system, (x) diseases of metabolism, (xi) diseases of the blood, spleen, and lymphatic glands, (xii) diseases of the alimentary canal, (xiii) diseases of the liver, gall-bladder, pancreas, and peritoneum, (xiv) diseases of the cardio-vascular system, (xv) diseases of the respiratory system, (xvi) renal diseases, (xvii) affections of the joints and bones, (xviii) diseases of the nervous system, (xix) psychological medicine, (xx) common diseases of the skin. A full index is provided

157 616-073 73
POSITIONING IN RADIOGRAPHY

by K. C. Clark. Fourth edition. London, Ilford, Ltd. and W. Heinemann (Medical Books), Ltd., 1945 526 pages, 1207 illustrations. 29 × 23 cm. £3 15s [£3 75]

Since its first publication in January 1939 this book has proved an outstanding and widely-appreciated work both for reference and for teaching the technique of positioning in medical radiography. It has most admirably achieved its stated object and more. It is a magnificently illustrated and a most comprehensive survey of the essentials relating to the practice of medical radiography, in so far as it concerns orientating the x ray tube, patient and film, presented in as nicely balanced a manner as could be desired

It is compiled by an author who has not only had a long, wide and varied personal experience but who has also enjoyed in full the valuable technical co-operation of many prominent radiologists and radiographers. Thus the material it contains is both authoritative and representative of the highest degree of collective modern knowledge of the subject

In all cases a photograph giving a general view of the patient's position in relation to the principal ray is shown, together with a typical radiograph resulting from such a positioning technique. Occasionally the technique is further clarified by recourse to line drawings and reference to dried-bone photographs. A set of exposure factors is given for each part and, although these are

restricted to the materials of a specified manufacturer and to the older types of x-ray film and deal only with the so-called "normal" patient, they serve as a valuable basis for estimating the conditions for other materials, heavier or lighter patients, and for the pathological cases

There is no attempt at discussion of apparatus although all the accessories in common use are mentioned and their function is well illustrated. This means that practically the whole of its 500 pages are devoted solely to positioning technique, with concise descriptions in simple language. It is refreshing to note here that, in spite of war-time restrictions, the quality of the paper is the same as that of pre-war editions, the technical quality of the illustrations and the layout of the book in general are of the highest quality.

As in earlier editions, the book is divided into small sections for easy reference. The material dealt with includes upper extremity, humerus and shoulder girdle, lower extremity, hip joint and upper third of femur, pelvic girdle, spine, bones of the thorax, skull, including general surveys, facial bones, maxillae, sinuses, glands and ducts, special techniques, arteriography, ventriculography and encephalography, heart and aorta, kymography of the heart and oesophagus, the respiratory tract, thymus gland, tomography of the lungs, the alimentary tract, gall-bladder, urinary tract, female genital organs, localization of foreign bodies, including several eye methods, dental surveys, soft tissue, brief accounts of myelography, stereography and cine-radiography, x-ray screen photography, seriescopy. Following the main body of the book is a supplement containing data on opaque media, notes on the exposure tables given, exposure technique on a representative mobile unit, exposure technique for x-ray negative paper and for non-screen technique. An index completes the work.

In this fourth edition the section on x-ray photography has been revised to bring up-to-date a rapidly progressing technique and much has been added to many of the other sections. It can confidently be anticipated that this book will remain a standard work of reference and will for many years to come prove a most valuable aid in the training of radiographers.

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616-73

THE STERILIZATION, USE AND CARE OF SYRINGES

by a Committee appointed by the Medical Research Council
Medical Research Council War Memorandum No 15 London,
H.M. Stationery Office, 1945 23 pages 25 x 15 cm 4d
[£0 016]

As is emphasized in the introduction to this memorandum, any risk, however small, will produce accidents if it is repeated often enough. Faulty injection technique—especially serious when it occurs in the course of mass inoculations or in hospital practice—has been responsible not only for mild inflammations and infections, but sometimes also for such conditions as streptococcal cellulitis and lymphadenitis, staphylococcal and streptococcal abscesses, tuberculosis, meningitis due to contaminated lumbar puncture needles, anaerobic infections such as tetanus and gas gangrene and systemic diseases like infective hepatitis and malaria. This small handbook has therefore been compiled from the experience of many workers and the results of extensive bacteriological tests, as a guide to methods which have been proved both safe and practicable for use in hospitals and for mass inoculations. It should be invaluable to those responsible for the instruction of medical students and nurses who must be made fully aware not only of the correct methods, but also of the risks which attend careless and imperfect technique.

The memorandum contains the obvious injunction that syringes used for the aspiration of septic material should never be used for an aseptic purpose, such as the injection of sterile medicaments. As there is no absolutely dependable method of sterilizing a syringe except autoclaving or heating in a dry oven at 160° C, one of these methods is recommended. Such a temperature would melt the cement at the glass-metal junction of the "Record" type of syringe, making the employment of such a syringe impossible. The memorandum does in fact strongly advocate the use of a two-piece all-glass syringe, and recommends that it should conform to the rigid specification laid down by the British Standards Institution for *All-glass hypodermic syringes*, No BS 1263 (1945). This specification has been specially compiled for syringes to be used in accordance with the instructions set out in the memorandum.

The contents comprise (i) introduction, (ii) the sources and avoidance of infection following injections, (iii) the choice of syringes and needles, (iv) instructions for sterilizing all-glass syringes, (v) disinfection of syringes by boiling, (vi) disinfection of syringes by means of alcohol and other chemical disinfectants, (vii) disinfection by the hot-oil method, (viii) mass inoculations, (ix) mass intravenous injections, (x) the care of needles, (xi) a syringe service for a hospital, (xii) the use of syringes for certain special purposes. Appendix A Disinfection with alcohol. Appendix B Methods of testing syringes for leakage. Appendix C References.

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616 13-089

ARTERIAL INJURIES

Early Diagnosis and Treatment

by the Vascular Injuries Sub-Committee of the M.R.C. War Wounds Committee. Medical Research Council War Memorandum No 13 London, H.M. Stationery Office, 1944 24 pages. 25 x 15 cm 4d. [£0 016]

For those whose experience of the early treatment of arterial wounds has been limited, this memorandum will afford a helpful guide to the morbid anatomy, clinical manifestations and prin-

ciples of treatment of such wounds and to the management of the ischaemic limb. Four appendices deal with the technique of arterial suture, the technique of administration of heparin, the technique of sympathetic block and the writing of case notes in vascular injuries. Readers interested in this subject should refer also to *British Medical Bulletin*, vol 2, No 7, which contains signed articles by several members of the Vascular Injuries Sub-committee on different aspects of this subject.

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616 71-0413

BONE-GRAFTING IN THE TREATMENT OF FRACTURES

by J. R. Armstrong Foreword by R. Watson-Jones Edinburgh,
E. & S. Livingstone, Ltd, 1945 175 pages, 204 illustrations
25 x 17 cm £1 5s [£1.25]

The first five chapters are devoted to a discussion of the subject in general. The various types of graft are described and the principal indications for the use of each are given. A brief survey of the management of these cases follows, together with a technical exposition of the method of cutting, shaping and fixing the grafts. The information is presented concisely, clearly and in adequate detail.

The section on chemotherapy will presumably be augmented in the second edition by the inclusion of a reference to penicillin. Rehabilitation is, surprisingly, dismissed in four lines. The author must have gained considerable experience of the value of the Rehabilitation Centre while serving in the Royal Air Force, and a separate chapter to describe the way it contributes to the patients' recovery would be helpful to others.

Mr Armstrong's originality and mechanical ingenuity are well shown by his approach to the problems of "screw fixation", he recommends the use of a Sherman self-tapping screw with an oblong head made to fit a box-spanner "screwdriver" instead of an ordinary head and screwdriver, and gives good reason for these modifications. He also advocates holding the graft in a sterilized vice and shaping it with a file.

The remaining fourteen chapters describe in turn the use of bone grafts in fractures of the spine, clavicle, upper limb and lower limb. The subheadings of each chapter are the same except for minor variations. They are entitled the indications for bone-grafting, the contra-indications to bone-grafting, the principles of operation, the pre-operative treatment, the operative technique and post-operative treatment. This uniformity makes it easy for the reader to find the information he seeks although there is a tendency for the section on the principles of operation to overlap that on operative technique. Some repetition could be avoided by combining these two.

The main themes running through all these chapters are the same, where external fixation is inadequate, apply internal fixation in the form of a bone-graft as well, where it is known that a bone-graft will be needed, apply it as soon as possible after the contusion has subsided. The author is to be commended on the fair and unbiased discussion of the place of bone-grafting in fractures of the carpal scaphoid, since he himself has had much to do with popularizing this method of treating this difficult injury.

Many orthopaedic surgeons will disagree with the advice to use Gill's "split-bone" technique for grafting fractures of the tibia, and some will refute the statement that "it is particularly undesirable to introduce metallic foreign bodies, in the form of plates or screws, around the ankle-joint for the purposes of internal fixation". In fact a screw gives very satisfactory fixation of a fracture of the internal malleolus and the technique is much simpler than if a bone peg is used.

A short but carefully written appendix, giving the necessary statistics, brings the subject of bone-grafting into its correct perspective in relation to the treatment of fractures as a whole. This addition is well judged, since it is almost impossible for the author of a monograph on this subject to avoid appearing somewhat over-enthusiastic. The high percentage of grafts used in fractures involving the posterior sub-astragaloid joint (42.9%) reflects his own preference for this method of treatment, perhaps he is well justified by the very indifferent results which other methods give.

The production of the book is up to the high standard that readers have come to expect of the publishers. There are a few colour photographs which are good by contemporary standards but illustrate that photographic methods which are adequate for advertisements in colour, are very far from meeting the naturalistic requirements of clinical photography.

Chapter headings (i) principles, general indications, contra-indications, (ii) types, sources, and fixation of grafts, (iii) pre- and post-operative treatment, (iv) operative technique, (v) cutting and preparation of grafts, (vi) fractures of the spine, (vii) fractures of the clavicle, (viii) fractures of the humerus, (ix) fractures of the radius, (x) fractures of the ulna, (xi) fractures of the radius and ulna, (xii) fractures of the carpal scaphoid, (xiii) fractures of the metacarpals and phalanges, (xiv) fractures of the neck of the femur, (xv) fractures of the shaft of the femur, (xvi) fractures of the tibia or fibula, (xvii) fractures of the ankle, (xviii) fractures of the tarsus, (xix) fractures of the metatarsals.

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RECENT ADVANCES IN NEUROLOGY AND NEUROPSYCHIATRY

by W. Russell Brain & E. B. Strauss Fifth edition London,
J & A. Churchill, Ltd, 1945 363 pages, 32 illustrations 20 x
14 cm. 18s [£0 9]

Although the first three editions of *Recent advances in neurology* were published under the joint authorship of Brain and Strauss,

the fourth edition was the work of Brain alone. In this fifth edition, the joint authorship is resumed, and the title is expanded to include neuropsychiatry. As the authors point out, neurology and neuropsychiatry have made greater progress in certain fields during the last four years than in almost any previous corresponding period, and this is reflected in the changes made in the present edition of this book. New topics included are electrical convulsant therapy for mental disorder, prefrontal leucotomy, peripheral nerve injuries, vasoneuropathy after chilling, neuritis of the shoulder girdle, two newly recognized forms of acute encephalitis, the use of penicillin for meningitis, and thymectomy for myasthenia gravis. The chapter on electroencephalography has been greatly expanded and now covers its applications to neurophysiology, sleep, epilepsy, and the psychopathies and psychoses. Much new material has been added on the vitamin deficiencies, intracranial sinus thrombosis, vertigo, sciatica and the herniated intervertebral disc, the treatment of meningitis with sulphonamides, myasthenia gravis, and disorders of bladder function. The chapter on brain injuries has been rewritten in the light of war experience. Each section contains the appropriate references to the literature. The book will be of great value to those who are interested in the recent progress that has been made in neurology, neuropsychiatry and neurosurgery.

Chapter headings (i) headache, (ii) intracranial tumour diagnostic methods, (iii) intracranial aneurysm, (iv) intracranial venous thrombosis, (v) meningitis, (vi) electro-encephalography, (vii) injuries of the brain, (viii) the treatment of head injury, (ix) the functions of the frontal lobe, (x) prefrontal leucotomy, (xi) electrical convulsant therapy (E.C.T.), (xii) the presenile dementias, (xiii) the hypothalamus, (xiv) sleep normal and pathological, (xv) the nervous control of micturition and defaecation, (xvi) neurotropic viruses, (xvii) demyelinating diseases of the nervous system, (xviii) nervous disorders due to vitamin deficiency, (xix) the peripheral nerves, (xx) disorders of the muscles, (xxi) sciatica and the herniated intervertebral disc, (xxii) the vestibular functions and Ménière's syndrome, (xxiii) miscellaneous clinical and therapeutic advances.

162 616.89 (02)

MANUAL OF PSYCHOLOGICAL MEDICINE

For Practitioners and Students

by A. F. Tredgold. Second edition. London, Baillière, Tindall & Cox, 1945 308 pages 22 x 14 cm. 18s. [£0.9]

The first edition of this book was reviewed in *BMB* 387/37. It contains a reasonably full account of the many forms of mental abnormality met with in medical practice. In the review of the previous edition attention was drawn to the writer's considerable acquaintance with the history and literature of psychological medicine.

The second edition follows little more than a year after the first. Besides careful revision, the new edition includes the following additions: the use of pitressin in the diagnosis of epilepsy, cerebral malaria, mental disorder due to vitamin deficiency, mental disorder in Parkinsonism, prefrontal leucotomy, alterations in the law regarding divorce in insanity and infanticide. A short bibliography has also been added.

163 616 957-083

VD LECTURES FOR NURSES

by R. H. Boyd. London, Heinemann (Medical Books) Ltd., 1945 24 pages. 19 x 13 cm 2s. [£0.1]

A very brief account of the venereal diseases and their management is given in this booklet, which is based on lectures for nurses. It is suitable also for midwives and those working in venereal disease clinics, ante-natal clinics and child welfare centres. The booklet contains four lectures: (i) syphilis, (ii) gonorrhoea, (iii) less common venereal diseases, (iv) practical notes (the avoidance of infection, how to take smears and blood samples, prostatic massage, heavy metal injections, sulphonamide therapy, local treatment).

164 617.3-083

FRACTURES AND ORTHOPAEDIC SURGERY

For Nurses and Masseuses

by Arthur Naylor. Edinburgh, E. & S. Livingstone, Ltd. 1945 283 pages, 243 illustrations. 22 x 14 cm 16s. [£0.8]

The author has written this book for the nurse who is already familiar with the general principles of surgical nursing. The book

demonstrates how these principles can be applied in the after-care of orthopaedic conditions. The more common conditions requiring orthopaedic intervention are described and the various forms of treatment are outlined. By this means the nurse and the physiotherapist are made familiar with the aim of the surgeon and the importance of proper post-operative treatment. The author says, "of the three essentials of treatment, prevention of deformity, correction of deformity, and maintenance of correction, the greatest of these is prevention," and he has paid particular attention to the prevention of deformity following the surgical treatment of diseases and injuries of the locomotor system. The book is particularly well illustrated with half-tones and line drawings and is one of the best of the many books devoted to special aspects of nursing. The author is resident surgical officer and medical officer in charge of the rehabilitation department of Westwood E.M.S. Hospital, Bradford.

Chapter headings (i) orthopaedic apparatus, (ii) orthopaedic theatre technique, (iii) general methods of correction of deformity, (iv) amputation, (v) fractures and dislocations, (vi) diseases of bone, (vii) diseases of joints, (viii) affections of the soft tissues, (ix) congenital deformities, (x) affections of the epiphyses, (xi) peripheral vascular lesions, (xii) the orthopaedic surgery of paralysis, (xiii) affections of the spine, (xiv) affections of the foot

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OPHTHALMIC NURSING

by Maurice H. Whiting. 4th Edition. London, J. & A. Churchill Ltd, 1945 133 pages, 56 illustrations 19 x 12 cm. 6s 6d [£0.325]

The author of this book is surgeon to the Royal London (Moorfields) Ophthalmic Hospital and the methods described are based on those employed at that hospital. Anatomical and physiological description is reduced to a minimum in order that as much space as possible can be devoted to the detail of special eye-treatment. As Sir John Parsons says in an introductory note, the practices adopted at Moorfields are the result of more than a century of experience and tradition. No better foundation could be used for such a book, and the author has produced a most useful little work upon a subject with which the opportunities for nurses and others to become acquainted are generally infrequent.

Chapter headings (i) anatomy and physiology, (ii) micro-organisms and their relation to disease, (iii) examination of the eye, (iv-vi) diseases of the eye, (vii) ophthalmic therapeutics, (viii) methods of treatment, (ix-x) operations, (xi) nursing of operation cases, (xii) nursing of non-operation cases, (xiii) minor operations, (xiv) eye nursing in schools.

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618 1 (02)

TEXTBOOK OF GYNAECOLOGY

by Wilfred Shaw. Fourth edition. London, J. & A. Churchill, Ltd, 1945 636 pages, 4 coloured plates and 271 illustrations. 22 x 14 cm. £1 4s [£1.2]

This book is intended for students preparing for final examinations, and in it particular attention is paid to the clinical aspect of gynaecology. The author, who is physician-accoucheur in charge of out-patients, St Bartholomew's Hospital, has included full descriptions of the anatomy and physiology of the female reproductive system, as he believes that future advances are most likely to emanate from these branches of the subject. Pathological descriptions have been reduced to a minimum.

In revising the text for this fourth edition, new work on endocrinology and chemotherapy has been included, while the chapter on diseases of the ovary has been brought up to date. In addition, 16 new illustrations have been added. This is an excellent short textbook of the subject.

Chapter headings (i) anatomy, (ii) normal histology, (iii) physiology, (iv) gynaecological diagnosis, (v) malformation of the female generative organs, (vi) specific infections of the female generative organs, (vii) diseases of the vulva, (viii) diseases of the vagina, (ix) injuries of the female genital tract, (x) diseases of the urinary system, (xi) the pathology of conception, (xii) pathology of pregnancy abortion, (xiii) pathology of pregnancy hydatidiform mole and chorion epithelioma, (xiv) pathology of pregnancy ectopic gestation, (xv) disorders of menstruation, (xvi) hormone therapy in gynaecology, (xvii) inflammations of the uterus, (xviii) prolapse, (xix) displacements, (xx) new growths of the uterus connective tissue tumours, (xxi) new growths of the uterus epithelial tumours, (xxii) radiological treatment in gynaecology, (xxiii) adenomyomata, adenomyosis chocolate cysts of the ovary, (xxiv) diseases of the ovaries, (xxv) inflammations of the uterine adnexa inflammations of the fallopian tubes and ovaries, salpingo-oophoritis, (xxvi) diseases of the broad ligament, fallopian tubes and parametrium.

FILMS

[Overseas medical teachers and medical societies who wish to borrow or purchase prints of the films indexed or reviewed here should apply to the nearest British Council representative (see inside back cover) or direct to the Editor, quoting the numbers used below, e.g. Film 6, *Inhalation of a film in this section does not imply that a print will be available for loan or purchase* In some cases it will be, and in others it will not.]

6 I.C.I. ANAESTHESIA SERIES No. 6 & 7 INTRAVENOUS ANAESTHESIA (Parts 1 & 2)

made by Realist Film Unit, 1944; owned by I.C.I., 16 mm sound, 1100 ft. [330 m]; 35 mm sound, 2760 ft. [830 m], 4 reels, black and white, 31 minutes

This film describes the technique and uses of intravenous anaesthesia. The first part shows in detail the technique of venepuncture, and this is followed by an account of the dosage of anaesthetic and how this should be regulated. The indications of the depth of anaesthesia are described and contrasted with those seen in inhalation anaesthesia. Laryngeal spasm is mentioned as one of the most important complications, and there is a clear demonstration of the treatment of this emergency. The treatment of paralysis of the respiratory centre, resulting from overdosage, is also shown. Various other dangers and some contra-indications to intravenous anaesthesia are also mentioned.

The second part of the film first shows the technique for administering an intravenous anaesthetic as a continuous drip infusion. It also deals with the various uses of this type of anaesthesia. The employment of this method in ophthalmic operations, general manipulations, as a basal anaesthetic, and as an induction before inhalation anaesthesia are also demonstrated.

A.F.C.

7 I.C.I. ANAESTHESIA SERIES NO 8 SPINAL ANAESTHESIA

made by Realist Film Unit, 1944, owned by I.C.I., 16 mm sound, 1240 ft. [370 m], 35 mm. sound, 3090 ft. [920 m], 4 reels, black and white, 35 minutes

This film deals with both the theory and practice of spinal anaesthesia. It starts with an excellent demonstration of the technique of lumbar puncture, showing the difficulties likely to be encountered and the ways in which they may be overcome. This is followed by a demonstration of the apparatus necessary to induce spinal anaesthesia and the types of anaesthetic which may be used. The techniques for the induction of a low or mid-spinal anaesthetic with heavy anaesthetic solution, and for high spinal anaesthesia with a light solution, are shown in great detail. A particularly ingenious feature is the demonstration of the action of anaesthetics varying specific gravity with the aid of coloured fluids in a glass model of the spinal canal. The importance of maintaining a constant watch on the blood-pressure is emphasized, and there is a concise account of the symptoms and treatment of anaesthetic poisoning. The film concludes with a demonstration of unilateral spinal anaesthesia and an account of various supplementary anaesthetics which may be used.

This useful film deals with almost every aspect of its subject in a remarkably short space of time, it will prove very valuable for teaching medical students and student-anaesthetists.

A.F.C.

8

STUDENT NURSE

made by G.B.I., 1943; owned by British Council; 16 mm. sound, 1,440 ft. [430 m]; 35 mm sound, 3,600 ft. [1,080 m]; 3 reels, black and white, 37 minutes

The purpose of this film is to show something of the training of state-registered nurses. It was made in a modern hospital and illustrates the working life of the nurse in wards, laboratories and lecture rooms and in more varied fields, including the casualty and x-ray departments and the operating theatre. The film also illustrates the facilities available during leisure hours in a modern nurses' home. Sequences are included showing some of the many branches of the nursing profession open to a state-registered nurse.

This film should be of interest to general medical and nursing audiences and to anyone interested in nursing as a career.

9

NEUROPSYCHIATRY¹

made by Spectator Short Films Ltd 1943, owned by British Council, 16 mm sound, 800 ft [240 m]; 35 mm. sound, 1900 ft. [1170 m], 2 reels, black and white, 20 minutes.

This film was made at one of the special centres of the Emergency Medical Service which have been organized for the diagnosis and treatment of war neurosis. The treatment is planned to restore the individual to maximum usefulness. On arrival, the new patient spends the first 24 hours away from the rest of the hospital. During this time specially trained members of the staff attempt to gain his confidence. His past history is taken and preliminary tests, both physical and psychological, are made. The further vocational and psychological tests he may undergo after he is transferred to the main part of the hospital, and various forms of treatment, including convulsive therapy, are illustrated. Organized games and exercises and various types of occupational therapy help to restore and maintain mental and physical health. In military cases, the doctor at the centre, together with advisers from the War Office, discuss and decide upon the most suitable vocational classification of the patient on conclusion of treatment at the centre.

¹ [This is an abbreviated version of a film made for the Ministry of Information and the Ministry of Health, the running time of which is 68 minutes.]

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PROFESSOR R. M. GORDON holds the Dutton & Walter Myers chair of entomology and parasitology at Liverpool University to which is attached the well known Liverpool School of Tropical Medicine. He was formerly professor of Tropical Diseases of Africa and director of the Sir A. L. Jones Research Laboratory at Freetown, Sierra Leone.

MR. K. UNSWORTH formerly held a research post endowed by Imperial Chemical Industries Ltd., at the Liverpool School of Tropical Medicine. He resigned this post on appointment as lecturer in parasitology in the University of Liverpool.

DR. J. R. BUSVINE has done research into the toxicological relationships of insects at the Stored Product Laboratories of the Imperial College of Science and Technology, and later at the Hawthorndale Laboratory of Imperial Chemical Industries Ltd. His work has laid stress on the importance of the relative resistance of different species of insect as a means of investigating the mode of action of insecticides. In 1940 he joined Professor P. A. Buxton, at the London School of Hygiene and Tropical Medicine to work on the control of lice. They developed the lethane hair-oil treatment for head lice, and were among the first British workers to test DDT. Since 1943 Dr. Busvine has been entomological adviser to the Ministry of Health. Apart from the comprehensive review that he has contributed, he has given frequent and valuable advice in the planning of this number.

DR. G. MACDONALD is director of the Ross Institute of Tropical Hygiene—the department of tropical hygiene of the London School of Hygiene and Tropical Medicine—and gained his experience of malaria control in Africa, India and Ceylon on the staff of the Liverpool School of Tropical Medicine, the Malaria Survey (now Institute) of India, and in private practice. He joined the Ross Institute early in 1939, but from the outbreak of war until very recently he was in the Army, where he became consultant malarologist first to Middle East Forces and later to the Central Mediterranean Forces. His published work, apart from the control of malaria, has been mainly on the epidemiology of the disease, and its effects on populations continuously exposed to it.

BREVET COLONEL SIR S. RICKARD CHRISTOPHERS, was a member of the Malaria Commission of the Royal Society and the Colonial Office (1898-1902), and from 1902 had a long and distinguished career in the Indian Medical Service, where he carried out and organized research on malaria and mosquitoes. From 1910 to 1922 he was in charge of the Central Malaria Bureau of India, and from 1922 to 1932 he was director of the Central Research Institute, Kasauli, India. On retiring from the Indian Medical Service, he was from 1932 to 1938, professor of malaria studies London University, and was in charge of the Experimental Malaria Unit at the London School of Hygiene and Tropical Medicine. He has

recently been engaged in studying repellents against mosquitoes at the zoological laboratories, Cambridge. He is the author of many publications dealing with malaria and kindred subjects.

LIEUT.-COLONEL H. J. CRAUFURD-BENSON is a parasitologist, who, before the war, was on the research staff of the Cooper Technical Bureau, Berkhamsted, working on the control of animal parasitic diseases more particularly on cattle lice and the nematode parasites of sheep. At the outbreak of war, in collaboration with Dr. J. MacLeod, he worked on the control of *Pediculus humanus corporis* de G., and this work resulted in the evolution of A. L. 63, the British Army louse powder. The details of the work will shortly be published in the *Journal of Hygiene*, earlier publication having been withheld for reasons of security. In 1942, Lieut.-Colonel Craufurd-Benson entered the Army as a louse expert to continue his researches on body lice, particularly on the development of new methods and with new insecticides, including DDT. In 1944, after working in Naples during the typhus epidemic, he turned his attention to the development of DDT as a general insecticide for use by the Army, especially for mosquito and fly control. In May 1945 he was recalled from Italy to become adviser in DDT at the War Office. In a recent honours list he was awarded the M.B.E. for services in Italy.

DR. R. LEWTHWAITE is a member of the Colonial Medical Service, and at the outbreak of war he was senior pathologist at the Institute for Medical Research at Kuala Lumpur, Federated Malay States. He was carrying on research into various aspects of scrub-typhus when the Japanese invaded Malaya, but he was fortunately evacuated with most of his material to Australia. He then came to England and was invited to join the Medical Research Council Typhus Committee. Shortly before the end of the war against Japan, he went to South-East Asia to lead a team of research workers in the study of the scrub-typhus problem under the auspices of the War Office and the Medical Research Council.

MR. A. E. H. HIGGINS trained as an entomologist under Professor J. W. Munro in the Imperial College of Science and Technology, where he later became a research assistant. He was for a time with the Australian Dried Fruits Board, where he learned the application of insecticidal spray control. He later assisted, under Professor Munro in carrying out a survey of the insect-infestation of stored foodstuffs storages, and transport throughout Great Britain. As a result of the survey, the Department of Scientific and Industrial Research, which shares with the Medical Research Council and the Agricultural Research Council the responsibility for British Government-controlled research, instituted its own Pest Infestation Laboratory in 1940 to undertake research on the biology and control of the insect pests of stored products. As a member of the staff of this laboratory Mr. Higgins was especially concerned with the control of insects infesting dried fruits. In 1942 he joined the Infestation Division of the Ministry of Food as mechanical methods control officer, and returned in 1943 to the Pest Infestation Laboratory to undertake urgent work, on behalf of the War Office, on the design and development of spraying equipment for use against insect vectors of disease.

PROFESSOR G. R. CAMERON, who contributes an article on the toxicity of DDT, was the subject of a note in No. 4-5 of the present volume of the BULLETIN.

REVIEW OF SELECTED PAPERS. Contributions to this section have been received from Mr. W. A. L. David, Mr. J. W. L. Beament and Dr. E. W. Prosser Thomas.

SPECIAL CONTRIBUTIONS

A REVIEW OF SCABIES SINCE 1939

R. M. GORDON, Sc.D., F.R.C.P. & K. UNSWORTH, M.V.Sc.

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Definition

Human scabies is usually defined as an invasion of the skin by burrowing mites belonging to the species *Sarcoptes scabiei*, but this definition may be extended to include those comparatively rare infections in man which are due to burrowing mites belonging to the genus *Notoedres*.

It is well known that many varieties of the species *S. scabiei*, which are normally parasitic on lower animals, may cause a transient infection when transferred to man. This type of infection is usually associated with the occupation of the individual, as in the case of "cavalry-man's itch," which is due to the transference of the equine form of the parasite. Buxton (1941) writes "In a similar way, men whose work brings them into contact with cattle or camels suffering from sarcoptic mange commonly acquire an infection, there are also records of its spreading to keepers in menageries from diseased llamas, kangaroos, chimpanzees, and other animals."

It is generally agreed that the differences in morphology which exist between the animal and the human forms of the

mite are minute and inconstant (Buxton, 1921), although Lunn (1944) states that he is able to distinguish between the equine and the human forms of the mite, and Vitzthum (1928) between the canine and human forms and those of other animals. The essential point of difference between the various forms, however, is physiological rather than anatomical, in that *Sarcoptes scabiei* obtained from sources other than man cannot maintain themselves for prolonged periods in the human host.

Geographical Distribution

Scabies has an almost world-wide distribution and was reported from every combat-zone in the recent war. Nothing, so far, in these reports suggests that the mite responsible differs in different localities in its life-cycle, in its habits, or in the lesions it produces. On the other hand, in civilized communities the disease usually receives far earlier treatment than it does in refugee populations or in native communities. In the case of native communities the presence

of the parasite is often masked by secondary infections which have frequently been described as clinical entities, in spite of the fact that attention has already been drawn to such errors by Blacklock (1924), who showed that *craw-craw* in West Africa was really untreated scabies, and by Backhouse (1929), who performed a similar service in regard to *kas-kas* in New Guinea

Importance

The importance of scabies in the army has been stressed by numerous writers. Sokoloff, referring to Napoleon's Italian campaign (1796-1797), wrote "Whole regiments of soldiers, the moment they were encamped for the night, threw off their knapsacks and scratched *en masse*. The officers suffered no less than the soldiers, their commander-in-chief was no exception, scratching himself with a vengeance, until blood appeared." It is unlikely that this reference to the commander-in-chief was intended to apply to Napoleon, nevertheless rumour has it that Napoleon suffered from scabies, and Friedman (1941), in his tome on scabies, discussed the problematical infection and its possible association with the traditional napoleonic attitude, which might be adopted for the scratching of a chronic left axillary infection!

Erasmus Wilson (1863) wrote "Since the return of the army from the Crimea the disorder (scabies) is revived. it has spread very extensively. Immediately upon the close of the war, scarcely a day passed without bringing me a case

of scabies, chiefly in the person of a military or naval officer." It is pleasant to record that Wilson was an exact observer and that later he noted that the higher incidence amongst the commissioned ranks may have been due to the fact that they were better able to pay his fee!

The literature concerning scabies in the war of 1914-18 is vast. We need only quote three representative statements.

Speaking of the important role which scabies played in interfering with the efficiency among the English Forces during the war of 1914-18, MacCormac & Small (1917) wrote "Every man incapacitated from duty—it matters not by what means—is a gain to the enemy. From the point of view of the army, and of military efficiency, those diseases ought to rank highest in importance which cause most 'casualties'. Judged from this aspect, diseases of the skin occupy one of the premier positions, for under the conditions of trench warfare it is inevitable that they are met with in large numbers."

Of scabies among the American Forces in the 1914-18 war, Lieut.-Col. Frank C. Knowles, consultant in dermatology to the American Expeditionary Force, wrote in 1919 "Approximately 40 per cent of all skin cases requiring treatment in the AEF were diagnosed as scabies."

Of scabies among the French Forces, Milian wrote in 1918 "Scabies is a veritable scourge in our armies. Its incidence is extremely high and it incapacitates a goodly number of soldiers. Scabies is as worthy of our attention as are the wounds of war, both because of the frequency of its occurrence and because of the complications which prolong its duration and affect its prognosis."

Scabies is not a notifiable disease, so that figures showing its incidence in the whole country during the recent war are not available. Samples from individual areas, however, furnish striking figures of the number of cases that were treated, at the cost of much time, at the various clinics. Thus the number of cases, both adults and children, treated at Corporation clinics in the city of Liverpool was 12,000 in 1941, 19,785 in 1942, 15,845 in 1943, 10,000 in 1944. In the British Army stationed at home, 6,000 fresh cases occurred monthly in 1942. It would appear, then, that Friedman accurately summarized the situation when he wrote "It is . . . no exaggeration to say that there never has been an extended war in which the unwelcomed *acarus* did not actively, joyously, and in great numbers participate."

Why is scabies important? In 1943, the director of hygiene in the Army made the statement that scabies was the most time-wasting disease of the Army in Britain. General Richardson now states (personal communication) that, since the abandonment in the British Army of hospitalization of cases and disinfection of fomites, much time has been saved, so that for the latter part of the war he believes that the statement should be modified to read "Scabies was one of the most time-wasting of the minor infectious diseases of the army." This description of scabies as a time-waster is essentially true. It wastes not only the time of the patient, but the

time of the medical staff who have to treat the patient, and the time of the men who, at any rate in the past, have had to disinfect the patient's belongings.

Incidence

It has already been shown that in the past a great increase in the incidence of scabies has followed closely upon the outbreak of any major war. This association is so well recognized that it has even led to the statement that all great rises in the incidence of the disease, both in the civilian and in the Armed Forces, are caused by war (Friedman, 1941). A fuller examination of the facts, however, indicates that scabies epidemics occur at intervals, and that a marked rise in the incidence of the disease may occur in the absence of hostilities. Thus, after the great epidemic of scabies which occurred during the 1914-18 war, the incidence of the disease fell until it reached and remained at the comparatively low figure of about 0.1% from 1923 to 1936 (Clayton 1944b). Mellanby (1941b), basing his figures on patients admitted to infectious diseases hospitals in five English cities, showed that in each of these towns there was a more or less steady rise in the incidence of the disease between the years 1937-39. On the other hand, the view that scabies increases in war-time is supported by evidence that, both during and after war, there is always an increased occurrence of the disease in both the civilian and the military population.

These two views are in no way contradictory, and we may combine and summarize them by saying that, although minor epidemics of scabies may and do arise independently of war, war usually results in an increased incidence of the disease above the pre-war level existing among the populations affected. That this is true of the present war can be seen by further reference to the rise already quoted. It is also true of countries outside England, as is proved by the statement issued by UNRRA in 1945. These figures are so interesting that they may be quoted in full.

"While war has always been destructive to the higher forms of life it has over and again proved a boon to the lower levels of organic life from body lice and down. During the present war, *Sarcoptes scabiei* has perhaps multiplied more rapidly than any other organism. Reports coming in from widely separated countries show that the increase is worldwide."

"At the hospital of Saint-Louis in Paris, which specializes in skin diseases, 9,859 cases of scabies were treated in 1939. A rise of the number of cases was noted immediately following the influx of refugees during the summer of 1940, and 24,559 cases were seen that year. In 1941, 65,875 scabies cases, and in 1942, 102,645 cases were treated in the hospital. In the course of only three years the increase was thus ten-fold."

"A report dated March, 1945, from the province of Aquila (Abruzzi) in Italy states that in the devastated towns and villages about 85 per cent of the population was affected by scabies, elsewhere 15 per cent on the average. Reports from other areas also speak of a rapid increase of scabies."

"Norway is one of the few countries where scabies has been notifiable for many years. The reporting can be considered good and is, at any rate, quite sufficient to show the rate of increase. In 1938, 9,605 cases were reported, in 1941, 24,477, in 1942, 37,439, and in 1943, 68,018. The increase was thus seven-fold."

"In Amsterdam, where the proverbial Dutch cleanliness kept scabies down to about 400 cases a year, there were over 30,000 cases in 1944—a 75-fold increase."

"In Finland, 10,993 cases of scabies were reported during the first quarter of 1945 as compared with 7,789 cases during the corresponding period of 1944."

"Medical journals of several other European countries have also referred to an alarming increase of scabies."

"Among refugees in Kweichow province in China nearly 100 per cent are reported to be infected with scabies."

These facts regarding the increase of scabies during the period under review are clear, but the cause of the rise in incidence is a subject of much dispute. It is generally agreed, however, that it is due to closer contact between individuals as a result of living under unusually crowded conditions. As Clayton (1944b) has written "In peace-time scabies is essentially a family affliction and tends to be limited, but in war-time the nation becomes the 'family' and scabies tends to be unlimited."

As regards the section of the community which is mainly responsible for causing the increase in the disease, little agreement has been reached. There is a tendency amongst the Armed Forces to blame it upon the civilian population, and numerous examples are quoted of the increased proportion of cases amongst soldiers returning from leave (Coleman,

1942, Ollerenshaw, 1942, Myers, 1944) During the 1914-18 war there was a tendency to take the opposite view, and to accuse the Armed Forces of spreading the disease amongst the civilian population, and some people hold the same view as regards the recent war. It must be remembered, however, that the importance of scabies during war-time tends to focus attention on the disease, and this leads to closer inspection of individuals, particularly when these are in uniform and subject to military discipline, so that it is probably true to state that, whereas the reported incidence amongst the Armed Forces falls but little short of the actual, the proportion of positives reported amongst the civilians falls well below the true facts.

So far we have referred to the incidence of scabies without differentiating between the types of communities from which the figures were derived. The figures for the Armed Forces apply, for the most part, to young adults living a communal life and more or less equally exposed to infection, whether by sexual contact or from any other source. The figures for the civilian population, on the other hand, are derived from a very large variety of sources, and it is obviously unnecessary to present figures in support of the statement that the proportion of cases found infected in the civilian population will vary according to such factors as the social stratum and the age of the individuals examined.

The high incidence of scabies in mental hospitals has been well recognized for many years, and during the course of the recent war some interesting observations have been recorded concerning the incidence of scabies in a community that is divided into various standards of intelligence.¹ Thus Hodgson (1941) submitted 100 unselected scabies patients and a control group of 500 consecutive recruits at an RAMC (Royal Army Medical Corps) depot to an intelligence test (Royal Eastern Counties Institution progressive matrices) with the following results:

Marks	Control	Scabies	Group
0-19	5%	27%	"very inferior"
20-26	19%	42%	"below average"
27-32	50%	28%	"average"
33-36	26%	3%	"above average"

Hodgson concludes that "subnormal and low-grade intelligence were found in great excess among the scabietic patients."

Mason (1941), commenting on these results, states that during the period 1926-36—at all events in the Navy—the source of scabies, both at home and abroad, was the inferior types of brothels and shore-side lodging-houses—places only frequented by the less-intelligent men. Mellanby, Northedge & Johnson (1942) repeated Hodgson's observations, but failed to confirm them. MacKenna (1943) believes that "Hodgson was correct in his general view that the incidence of scabies was greater in troops of low mentality than in individuals more favoured mentally, but because of Hodgson's use of norms derived from RAMC recruits, it is possible that the figures obtained in this group were too high and consequently the number of cases which appeared to fall in the lowest intelligence group were exaggerated." MacKenna supports this statement by figures supplied by Hargreaves, showing the incidence of scabies among approximately 40,000 recruits who were graded according to their intelligence. These figures show an almost steady rise in the incidence of scabies with declining intelligence.

The high incidence of scabies amongst certain sections of the population is presumably due to the fact that their habits tend to expose them to a greater risk of infection. Quite apart from this question of exposure to risk, however, it is sometimes stated that certain individuals are less prone to acquire the disease, even when exposed to the same risk as their fellows, and are therefore credited with some degree of natural or acquired immunity.

Immunity

In the past it was often suspected, but never proved, that some degree of immunity against scabies was acquired as a result of previous infection. That an individual suffering from a second attack of scabies is more likely, without treatment, to rid himself, at any rate partially, of the parasites than is one suffering from a first attack, has now been suggested by Mellanby (1944a). In this important paper Mellanby shows that the invasion of the corneum at the first attack of the mite results in no greater reaction than might be expected to follow the introduction of any foreign body of a similar size. He goes on to show that persons suffering from a primary infection, after a period of one month from the time of the first invasion, become sensitized to the parasite, and from that period onwards itching and other symptoms develop. At the first infection a parasite-rate of 25 adults may be reached in 50 days, and up to 500 in 100 days, after this the number of mites decreases rapidly. In contrast to these primary cases, persons who have previously suffered from scabies notice itching at the site of infection within 24 hours, while, subsequently, the mite population seldom rises to a fraction of the height reached in the first infection. Mellanby attributes this ability of the sensitized individual to rid himself of the parasites to three reactions: "(a) scratching by the host which removes the parasites mechanically, (b) oedema renders the cuticle unsuitable for colonization and causes the mites to vacate their burrows, (c) scratching produces sepsis which is fatal to *Sarcoptes*." The present reviewers suggest that the words "intolerance to the parasite" might be substituted, with advantage, for the term "partial immunity" applied by Mellanby.

Life-cycle and Population

It is a remarkable fact that, in spite of the wealth of investigations concerning human scabies which have been made in recent years, little has been added to the account of the life-cycle of the parasite as given by Hebra (1868). Indeed, it would appear that Hebra's original account has, for the most part, been disregarded by later workers, although no new facts have been discovered which would throw doubt on the accuracy of his observations. On the contrary, the only original account of the life-cycle of the burrowing mites which has appeared during the war period (Gordon, Unsworth & Seaton, 1943), although differing in unimportant details, agrees well with Hebra's description of the life-cycle of *Sarcoptes scabiei* var. *hominis*. These authors, as a result of their observations on *Notoedres* infections in rats, were able to give a full description of the life-cycle of the mite, a description which may be summarized as follows: "Having hatched out from the eggs laid by the female, the majority of the larvae escape from the parent tunnel and wander on the skin, but a proportion remain in the parent tunnels or in side-pockets off the tunnels, where they may continue their development, at least as far as the nymphal stages. Of those which reach the skin surface, many perish without further development, a minute proportion are transferred to new hosts, whilst the remainder burrow into the intact stratum corneum to construct their almost invisible moulting-pockets. Once established in its minute pocket the larva makes no attempt to extend it, but feeds and grows within its narrow limits until it is ready to cast its skin and become a nymph. The resultant first nymph either remains in the larval pocket or leaves it to construct a similar pocket in another area. In either case it moults again within the pocket to become the second nymph, which behaves similarly to the first, either remaining in the pocket or leaving it to construct a duplicate refuge in which the final moult occurs, resulting in the production of the adult male or female. It follows from this account that any or all of the three moults undergone by the developing mite may occur in the original larval pocket. This process of development from egg to adult life occupies some 17 days. The adult female remains quiescent in the moulting-pocket until she is fertilized by the nomadic male, which usually reaches her by tunnelling through the wall. Once fertilized, she extends the moulting-pocket to a tunnel, in which the first eggs are laid 4-5 days later. The tunnel is now enlarged to form the conspicuous, tortuous breeding-gallery in which she lays her eggs at the rate of 3-4 a day. The adult male, having left his moulting-tunnel, lives mainly on the surface of the skin, but occasionally penetrates it, either for the purpose of obtaining food or to fertilize the female."

¹ [See also review by Dr. R. Slater, in the previous issue of the Bulletin (BMB 74)—Ed.]

Until 1942, references in the literature to the numbers and proportions of the different stages of mites causing sarcoptic mange in man and animals were scanty. In 1942 Johnson & Mellanby, and in 1944 Bartley & Mellanby, recorded the results of their observations on the numbers of adult female *Sarcoptes* occurring in the skin of the human host, while in 1943, Gordon, Unsworth & Seaton published figures for the numbers and stages of the mite-population occurring among rats infected with *Notoedres*.

In the case of human scabies, Johnson & Mellanby (1942) have shown that, contrary to previously accepted beliefs, the number of ovigerous female mites occurring on an infected individual is relatively small. Among 886 cases examined, the average mite population was 11.3 per person, 52% of the cases had under six mites, and only 3.6% had over 50. In a later paper Mellanby (1944a) ascribes the high rate of infection in certain cases to the result of a primary infection occurring before the establishment of immunity. Johnson & Mellanby (1942) made no reference to the number and stages of mites other than adult females, but in a later work Mellanby (1943) writes "Eggs and immature stages of *Sarcoptes*, though difficult to find, are probably much more numerous than ovigerous females."

As regards animal scabies due to *Notoedres*, Gordon, Unsworth & Seaton (1943), as a result of examining more than 1,000 mites collected from a known area of skin, showed that, at the time of observation, 85% of the total mite-community were living a subsurface existence, whereas 15% were living a free existence and moving about on the surface of the skin. They further showed that the constitution of this free, actively moving, surface population was quite different from that of the subsurface. Whereas the adult and ovigerous females made up 40% of the subsurface population, not a single mite at this stage of development was recorded amongst the free-living population, which was made up of 90% larvae and 10% nymphs and adult males.

Munro (1919), at the close of the 1914-18 war, wrote "In the literature relating to scabies and to the itch mite no two accounts of the life-history of the mite agree and there is a similar difference of opinion regarding its mode of spread or dispersal." At the close of the recent war, opinion still differs regarding the life-cycle and also, as will be shown in the next section, as regards the transmission.

Transmission and Survival off the Host

Scabies is spread from one individual to another by the transfer of the mite causing the disease. This transference is generally accomplished as a result of direct contact between infected and uninfected persons, the risk of infection depending on the closeness of the contact. Thus scabies is often spoken of as a venereal disease, but it would be more appropriate to call it a family disease, in which infections are spread from husband to wife, from mother to child, and so on.

As regards indirect transference, although some writers still hold the view that disinfestation is essential, Mellanby (1941a, 1942) has expounded the view that the risk of infection resulting from the use of blankets, underclothes, etc., previously used by an infected person, is slight—a view which has received support from many other workers and has been endorsed by the fact that, since the publication of Mellanby's work, the Ministry of Health (1943) has decided that "routine disinfestation of clothing is unnecessary, as the layer of medicament which covers the body after treatment is usually sufficient to kill all mites on the clothing." A similar abandonment of disinfestation has been adopted by the British Army. It would appear, however, from recent publications (Moyes, 1941; Brain, 1943) that this statement must be received with some caution, and that in place of the word "unnecessary" should be substituted the expression "incommensurate with the expenditure of labour involved." Thus Mellanby, Johnson, Bartley & Brown (1942) state "Experiments on the infectivity of blankets and clothing (Mellanby, 1941a, 1941b, 1942) have suggested that the importance of these in the transmission of scabies has generally been overestimated. Nevertheless, infection by fomites does occasionally occur, and therefore disinfestation may sometimes be advisable." As regards the type of fomites most responsible, it is generally agreed that the more intimate the contact, the greater the chances of transference, thus underclothing is more dangerous than the coat, sheets more dangerous than the blankets, and so forth.

If we accept the view that the transmission of scabies sometimes occurs through fomites, the length of survival of the infective stage of the mite off the host is obviously of some importance. No figures are available for stages other than the adult, but Mellanby, Johnson, Bartley & Brown (1942), working with adult females removed from the corneum, showed that at 13° C and 90% relative humidity the majority of mites died within a week, but a few remained alive up to 14 days. These figures correspond approximately to the survival of infective *Psoroptes*, one of the causes of mange in sheep. Thus the Survey Committee of the National Veterinary Medical Association (1944) reports that "In repeated attempts to produce infection from contaminated pens—carried out in South Africa, America, Germany and Britain—successful transmission was achieved only when the interval between contamination and exposure was under 9 days, and usually only when the exposure occurred without delay."

As regards the stage of the mite responsible for transmitting the disease, Mellanby and his colleagues believe that this is accomplished by the transfer of one or more adult, fertilized, female mites from the infected to the non-infected host. Gordon, Unsworth & Seaton (1943), basing their remarks on the result of a large series of animal experiments, show that the disease is transmitted by the surface population, either larvae or nymphs, and that, whilst it is a matter of considerable ease to transmit the disease with as few as five larvae, it is only in a few instances that transmission can be accomplished by the transfer of adult female mites. They suggest that this is probably also true in the case of human scabies, and that the immature stages of the mites, which are essentially surface-living and are responsible for the spread of the disease on the host, are much more likely to be responsible for its transmission than the adult female mite which rarely quits its burrow.

Sites attacked, Clinical Manifestations, Diagnosis

Before the recent war-time research, there was a tendency among medical men to assume that the whole of the eruption of scabies, both burrows and "rash," which involve certain well-defined areas of the body, such as the hands and arms, abdomen, buttocks and genitalia, were caused directly by the invasion of the cuticle by the mite or its immature stages. Much confusion has resulted from this failure to distinguish clearly between the burrows caused by the excavations of the adult females and the so-called scabies "rash," of which the cause has not yet been fully explained, but of which the appearance and distribution differ markedly from that of the burrows.

The "burrows" It is a well-known fact that female mites, when confined under a watch-glass, will burrow anywhere (Buxton, 1941). Under such circumstances, the female may later leave her enforced home to seek a more congenial site, as was noted by Munro (1919) and confirmed by Mellanby (1943). When left to make her own selection, she tunnels wherever the skin is soft and wrinkled, or folded as at the joints. Thus, in babies burrows occur much more commonly than they do in adults on sites such as the face, soles of the feet and palms of the hands (Buxton, 1941; Johnson & Mellanby, 1942; Bartley & Mellanby, 1944).

Johnson & Mellanby (1942), basing their observations on an examination of the adult mite-population among 886 infected adult males, have shown that the majority (63%) were found on the hands and wrists, 10.9% on the extensor aspect of the elbows, 9% on the feet, 9% on the genital organs, 4% on the buttocks, and 2% on the axillae, the remaining 2% occurring on the rest of the body-surface. In the case of the adult female, the distribution of the mites has not been so fully observed, but it appears to be similar, except that burrows occur more commonly on the palms of the hands and on the breast than they do in the adult male (Bartley & Mellanby, 1944).

The "rash" As already stated, the distribution and appearance of the so-called "rash" differs markedly from that of the burrows. The burrows are recognizable as thin, sinuous lines, each a few millimetres to several centimetres in length, housing the adult females, their eggs, larvae and faeces, while sometimes one or more vesicles may be found underlying the floor of the tunnel. The rash of scabies, on the other hand, consists of a follicular, papular eruption, which tends to spread in a circular manner. Individual papules may, and often do, occur along the lines of the burrows, but, in

addition, they are widely distributed on areas which rarely harbour the burrowing female, such as the front of the abdomen, the front and inner aspects of the thighs and on the buttocks. Another point of differentiation is that, whereas a careful examination of the burrows normally furnishes evidence of present or past occupation, examination of the papules forming the rash is commonly devoid of any such result. In spite of this, some authors hold that these papules are caused by the penetration of the migrating larval stages (War Office, 1941, Clayton, 1944a).

During the period under review, the relationship between the burrows and the rash has been fully investigated by various workers, notably by Mellanby (1944a), who studied the development of the infection in human volunteers, and his work has been supported by Clayton (1944a), who watched the development of a primary infection on himself.

The views of these investigators may be summarized by saying that the tunnels, no matter how numerous, produced by the adult females, are never responsible for the irritation and the associated rash until the patient has become sensitized to the infection—a process which requires at least some weeks for its development. Thus Johnson (1943) writes "From an inspection of patients there appears to be no relation between the intensity of infection—i.e. the number of parasites, and the severity of the accompanying clinical symptoms. The man mentioned above as having 511 mites showed quite a mild papular eruption and had so little irritation that he did not report himself sick. A patient with an average infection of a dozen mites, or less, may, however, suffer severely and possess widespread and intensive erythema. Thus cases are sometimes spoken of as being 'heavily infected'—whereas what is really meant is that the clinical manifestations are severe."

"The time which elapses after infection, before the rash and irritation become obvious or well marked, may be as much as six weeks. It is safe to say that obvious and generalized symptoms do not usually show up before one month has elapsed. But the latent period and the intensity of the symptoms would be expected to vary with the individual and perhaps with the degree of infection during the latent period."

Mellanby (1944a) corroborates Johnson's finding that the itching in scabies does not commence until the infection is well advanced, and suggests that the irritation, so long thought to be caused by the active movements of the burrowing mites, is, in reality, due to a tissue-reaction resulting from the sensitization of the human host to some protein constituent or product of the invading mite. This author has been able to obtain positive intradermal reactions by using a saline extract of the mite as antigen. Positive reactions were obtained only in cases of scabies of more than six months' standing, the apparent time-lag between the development of clinical evidence of sensitivity and of a positive reaction to the intradermal test being explained by the fact that production of the antibody is slow, "so that although sufficient sensitization to cause irritation in the presence of the *Sarcoptes* may arise within a month or six weeks the sensitization becomes progressively greater, and it is only after six months that it is sufficiently great to react markedly to an extract of the type that we used."

The itching which always develops in the later stages of scabies inevitably leads to scratching, and this renders diagnosis more difficult, not only as a result of the mechanical removal of a proportion of the mites from their burrows, but also because the scratching is often followed by secondary infections which mask the true nature of the disease. Under these circumstances, if we omit the intradermal injection of antigen, the reaction to which develops too late to be of any practical value, a certain diagnosis of scabies can be founded only on the finding of some stages of the mites or of their eggs in the tissue of the host, and nothing has been described during the war years which suggests any simpler or less laborious method. Nevertheless, there is little doubt that in the future, as in the past, the diagnosis of scabies by the general practitioner will continue to rest, in the vast majority of cases, on clinical observation.

Treatment, Including Preparation of the Patient

The preceding portion of this review has been concerned almost solely with the biology of the mite, and the reader may find himself in agreement with Leyton (1941) "that present ideas are tending too much to the academic and

theoretical. After all, provided the patient obtains benefit and relief, what matter to him the *modus operandi*?"

The present reviewers' file, which is far from complete, contains some 500 summaries of articles and letters dealing with scabies, roughly, the sections consist of some 450 references to treatment and some 50 references to the biology of the mite. Nevertheless, it is from the comparatively small body of literature dealing with the biology that we have learned the all-important fact that, whereas there are quite a large number of effective sarcopticides, none of these can be relied upon to cure the patient, much less to prevent the spread of the disease, unless they are properly applied.

As regards the method of application, all authors are agreed that the essential criterion for success is that every portion of the patient's skin, except the head and neck, must be covered by the sarcopticide. It is probably true to say that it is lack of attention to this single point which has for so long justified the statement of an eighteenth-century writer that "Scabies is an easily cured disease, but physicians rarely cure it." While the application of the drug, in the opinion of the majority of authors (Ministry of Health, 1940, Fessler, 1941, Johnson, 1943, Mellanby, 1943), is best carried out by a trained staff, complete success has been claimed when the infected person is allowed to apply the medicament himself (Corfield, 1945).

As regards the preparation of the patient, whereas all authorities are in agreement regarding the necessity of treating the whole area of skin liable to infection, considerable differences of opinion exist regarding the importance or otherwise, of a preliminary bathing and scrubbing of the skin. These vary from the view expressed by Dixon (1941) that cases of scabies may be completely cured by bathing and scrubbing without the use of a sarcopticide, to that of Mellanby (1943) who states "Experimental work has shown that equally efficient cures are obtained when the bath is omitted, though, as so many scabies patients are rather dirty, it is advisable to give the bath for hygienic reasons." This remark is couched in somewhat stronger terms than that made in a paper by Mellanby, Johnson & Bartley (1942) in which a similar statement was qualified by the words "In spite of this, however, it is desirable that before applying a parasiticide the body should be soaked in a hot bath and rubbed well with soap, as this may enable the medicament to penetrate the skin more readily."

Silcock (1940), Bigham (1941), Fessler (1941), MacCormac (1943) and the Ministry of Health (1940, 1942) all recommend a preliminary bathing and scrubbing, whereas, Lunn (1942), Johnson (1943) and Geffen (1944) all support Mellanby's contention that it is not essential. Gordon & Seaton (1941), as a result of examining a series of sections cut from the skin of infected animals previously treated with sarcopticidal drugs, showed that "Preliminary washing and scrubbing of the infected areas opens up the burrows, removes many of the mites and their eggs, and increases the penetration of the drugs into the burrows." On the whole, it would appear reasonable to believe that, whereas a high proportion of cases of scabies is cured by the use of benzyl benzoate without preliminary bathing or scrubbing, the efficacy of this or of any other form of treatment is enhanced by the preliminary preparation of the patient, by bathing and scrubbing (the term "scrubbing" being used in a mild sense).

The British Pharmacopoeia begins with the drug Acacia and ends with the drug Zingiber. Apparently neither of these has been used in the treatment of scabies, but an astonishing number of others have, and the users claim to have obtained surprisingly good results with the most unlikely materials. Not only has a large number of drugs been advocated, but the literature concerning some of those in common use and the most suitable bases in which to incorporate them is so great that it is obviously impossible to deal with them in the space at our disposal, particularly since many of them are contradictory in character.

Gordon & Seaton (1941, 1942) and Mellanby (1943) have reviewed the literature on this subject, and little has been published since the appearance of their papers to add to the situation.

If we omit from consideration dimethyl thianthrene (mitgal), concerning which little has been published during the war years because supplies have been short, we are left with three drugs of proved efficacy.

Inorganic sulphur. This drug is usually prescribed in the form of an ointment containing 2.5–10% of sulphur. It has for many centuries been recommended, with good reason,

as a specific in the treatment of scabies. It is a highly efficient sarcopticide, but it suffers from a dual disadvantage in that it is liable to produce dermatitis if improperly used, and is usually prescribed in the form of an ointment, which is uncomfortable to the patient and damaging to his clothes. There has been a general tendency during the past six years to abandon this form of therapy for the following more-recently introduced treatments.

Benzyl benzoate At the present time benzyl benzoate ranks high in popular favour as a cure for scabies. Its use was first advocated by Kissmeyer in 1937, who drew attention to the rapidity of the treatment and the small relapse-rate which followed its use—observations which have been amply confirmed by later workers, notably by Mellanby, whose careful and detailed work on the subject has added greatly to our knowledge. The drug has a dual advantage in that it can be rapidly applied and does not damage the clothing. Whilst cases of dermatitis have been recorded as a result of its use (Buchanan, 1940, Warren, 1940, Buchan, 1941), particularly among young children, the risk of such sequelae has been largely eliminated by the substitution of watery emulsions of the drug for the former soap and alcohol mixtures (Mallen, 1942, Mellanby, 1943). Occasional cases of dermatitis, however, still occur (Daughtry, 1945).

Tetraethylthiuram monosulphide During the war period only one new drug has been introduced and proved successful for the treatment of scabies. Tetraethylthiuram monosulphide (tetmosol) was first brought to notice by Gordon & Seaton (1941) and has proved to be a very efficient sarcopticide, although the observations recorded following its use are not yet sufficient to allow for comparison being made between the relative values of tetmosol and benzyl benzoate. Percival (1942) found that he was able to cure 100% of cases with two applications daily for three successive days. Clayton (1943), using a 5% solution, found that 59% of cases were cured by three applications, made at intervals of one to two days, the remaining 41% of cases requiring more than three applications to produce a cure. Bradshaw (1944), however, found that the drug in a 6.25% concentration cured 97% of cases of scabies after three applications made on successive days. He recommended it as the treatment of choice for children, the application being painless even on abraded areas. Wilshaw (1945) claimed 100% cures among some 350 cases treated with tetmosol. In no instance, however, was the number of treatments less than four, while the strengths of tetmosol used apparently varied from 5% to 25%.

Prophylaxis

The increase in the incidence of scabies, which began during the years immediately preceding the war, raised the question of whether some method of prophylaxis could not be found. Thus Mellanby (1944b) stated: "With our present knowledge there should be little difficulty in treating and curing all cases of scabies as soon as these are diagnosed, but a great advance would be made if we could discover a method of scabies prophylaxis which would prevent infection from taking place." This author went on to describe a series of attempts to control the spread of scabies by the treatment of

already-infected individuals with benzyl benzoate. Eight hundred and four patients living in a closed community (a mental hospital), among whom the incidence of scabies had been determined, by sampling, to be 26%, were treated on two occasions with benzyl benzoate. After this treatment, in the words of the author, "Scabies has given no further trouble." That it was not entirely eliminated, however, is suggested by his subsequent remark: "only a negligible number of cases has been found." In view of the uneconomical nature of such a method of control, Mellanby adopted a suggestion of Johnson (1943), who wrote: "It may be said that if all the mites on the hands and wrists of all patients alone could be killed (e.g. by dipping in benzyl benzoate solution), then about 60 per cent of all the parasites would be eliminated. This might have a progressive and great effect on the reduction of the disease." The hands and wrists of 13,000 school-children were treated on twelve occasions at fortnightly intervals, after which the incidence of scabies had fallen by 54% in one group, but only by 15% and 28% in the other two groups. The conclusion reached was that "the extra trouble and expense of providing benzyl benzoate were very meagrely repaid." It was at one time hoped, and indeed popularly believed, that the wearing of DDT-impregnated clothing and the use of DDT powder protected the individual against scabies. That this is not the case, unfortunately, has been shown by Hellier (1945).

Davey, Gordon & Unsworth (1944) and Gordon & Unsworth (1944), as a result of a large series of animal experiments with soap impregnated with tetmosol, showed that it acted as a complete prophylactic when used to protect against animal scabies, while Gordon *et al.* (1944) showed that, when used for bathing, it cured a high proportion (80%) of established cases of the disease in man. As a result of these observations, they recommended its use as a prophylactic in human communities exposed to scabies.

Subsequent trials in human scabies have amply justified the conclusions reached by these earlier workers, and the value of the soap as a prophylactic is now established. Mellanby (1945) has been able to show that 10% tetmosol soap, when used as a substitute for ordinary soap by members of a closed community, not only prevented the development of any new cases of scabies, but reduced the incidence of scabies among the infected population in a mental hospital from 13.2% to 1.3% in eleven weeks. Continuing the work of Mellanby and using 5% tetmosol soap, Bartley, Unsworth & Gordon (1945) showed that the incidence of scabies, which, in a similar community, had risen from 4% to 9.2% in 18 weeks, had fallen to 0.5% 13 weeks after the introduction of the soap, and that only one new case occurred, showing that, even in this relatively low concentration, the medicated soap had remarkable powers, both as a prophylactic and as a curative agent.

The tendency of the drug to produce dermatitis appears to be slight, cases which have occurred being mild and quickly subsiding when its use is discontinued. Only three cases of dermatitis occurred among 705 patients who used 10% tetmosol soap, for a period of 11 weeks. No cases of dermatitis have been recorded following the use of 5% tetmosol soap.

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¹ [BMB 78]

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RECENT WORK ON THE LOUSE (*Pediculus humanus* L.)

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The two varieties of the human louse, *capitis* and *corporis*, are very similar in their anatomy and physiology. But the difference in their habits, which induces one form to inhabit the scalp and the other to live amongst the underwear, results in two quite separate problems of public health. These problems are most distinct in the more modern countries, where improved standards of hygiene (especially the regular laundering of underwear) have relegated the body-louse to a minor problem in peace time. The people infested by it are mainly vagrants, transitory inhabitants of the casual ward or common lodging-house. They are often elderly and sometimes infirm.

The head-louse, on the other hand, is disturbingly common in some industrial areas. It attacks quite a different section of the population, mainly girls and young women, often of quite cleanly habits. Sometimes, indeed, the parasite has benefited from a misguided vanity, when regular combing of the hair has been neglected in order to preserve the set of a "permanent wave"!

With the advent of war, the status of the two problems was changed. The destruction of towns, the disturbance of amenities, famines and mass movements of people caused by war have always given the body-louse a chance to spread rapidly and cause epidemics of typhus and other rickettsial diseases. It appears that, under experimental conditions, both races of louse can transmit typhus, but the major epidemics of the past have all been associated with widespread *corporis* infestation. The almost complete absence of typhus from north-western Europe, where *capitis* is still comparatively frequent, is another ground for assigning to *corporis* the major role in the spread of the disease.

A. CONTROL OF THE BODY-LOUSE PREVENTION OF TYPHUS

Since the danger of typhus is greatly increased by war, much of the research on the subject has been done during the two great wars of this century. During the war of 1914-1918, the researches of Bacot, Keilin, Nuttall and others, largely elucidated the biology of the louse, during the recent conflict, most of the progress has been towards securing effective control of the parasite. Recent papers on the biology of lice include an account of their sensory physiology and behaviour (Wigglesworth, 1941) and studies on the influence of nutrition and temperature on their longevity and oviposition (Leeson, 1941a, 1941b, Haddow, 1941). The advances in control-measures will concern us for the rest of this article.

One of the most valuable innovations is the development of anti typhus inoculation on a mass scale. The various vaccines have given evidence of protection from the disease and they certainly make it much less severe. It is, therefore, much safer to attack a typhus epidemic, because all medical and sanitary staff can be immunized. Even whole armies

exposed to special risk can be treated, the Allied soldiers in Naples escaped the disease partly for this reason. Inoculation, however, is too slow to check a really large epidemic and, so far, there appear to be no drugs of therapeutic benefit by the time that a patient shows symptoms of typhus (Andrewes, King, van den Ende & Walker, 1944). Therefore, we must still rely, to a large extent, on attacking lousiness to quell an epidemic.

In all the great wars of the past, the soldiers became chronically lousy and were usually the victims of terrible typhus epidemics which sometimes paralysed whole armies. But now that the strategic importance of disease is realized, the hygiene of troops has been greatly improved and military epidemics are much less likely. So the advances in methods of controlling the louse are most likely to benefit civilians in areas devastated by war. The halting of the Naples epidemic was the first example of this.

Experimental Methods

To find new methods of controlling the louse, it is almost essential to keep a culture for laboratory experiments. Body-lice can be bred satisfactorily only by allowing them to feed regularly on man, though a recent American paper proves that they can be reared, with difficulty, on rabbits (Davis & Hansens, 1945). In England we employ the method of breeding them in small boxes with gauze bottoms through which the lice can feed. These are firmly attached to the skin of the leg during the day, which gives the lice opportunity to feed at will during 12 to 16 hours out of the 24 (Buxton, 1940e). Similar boxes, but made of metal so that they can be thoroughly cleansed, are used for experiments. In a method employed in America, the lice are kept in an incubator at 30° C and fed twice daily on men employed for the purpose. This procedure is slightly more artificial than ours, but a very large culture of lice can be maintained by it, for it is stated that as many as 40,000 lice can be fed on the back of one man without great discomfort (Culpepper, 1944).

Before new insecticides can be recommended, practical trials are necessary. In Britain we have done tests on naturally-infested men, living their normal lives, and only coming at intervals for inspection. Usually only one garment would be treated, which implies a fairly severe test, for the men were constantly exposed to re-infestation from other garments and from their associates and surroundings (Craufurd-Benson & MacLeod, 1946, Busvine, 1945). Similar field-trials were done under semi-tropical conditions with native labour gangs in Egypt (Buxton, unpublished) and in jails in Algiers (Craufurd-Benson, unpublished).

In the course of these trials, opportunities arose for studies of body-louse populations under natural conditions. A great deal was learnt about the distribution of lice among the undergarments, the proportions of the different stages present, and the fluctuations of numbers of lice which may occur on

over short periods (MacLeod & Craufurd-Benson, 1941b) Examinations of beds in common lodging-houses revealed the numbers of lice to be expected in the beds after infested men had slept in them (MacLeod & Craufurd-Benson, 1941a), and some simple experiments were made to trace the meanderings of lice among the clothes (Busvine, 1944a)

Much of the American fieldwork was less naturalistic, since it was done with artificially-infested men (Davis & Wheeler, 1944, Jones, McAlister, Bushland & Knipling, 1944) This has certainly the advantage of convenience, for much time and trouble are wasted with naturally-infested vagrants by frequent disappearances during the course of the experiment One group of Americans, however, studied the difficulties of control under entirely natural conditions by attempting to eradicate lice completely from village communities in Mexico (Davis, Juvera & Lira, 1944)

The final testing-grounds for anti-lice measures are, of course, the sites of actual epidemics of lousiness, especially with typhus present Most publicized of these practical demonstrations of modern delousing methods was the attack on the outbreak of typhus in Naples in 1943-44 Other successful campaigns have been accomplished by the Russians in Moscow (winters 1942 and 1943), and in Bessarabia, and by the French in Algeria (Sergent & Beguet, 1944)

Advances in Control Methods

Hot-air Disinfectors

Disinfestation of garments by hot air is a convenient method which was widely employed during the previous war Its advantages are ease, cheapness and safety, and simple hot-air disinfectors (such as the Orr Hut and the Serbian Barrel) can easily be improvised in the field A recent Russian paper describes further easily-constructed disinfectors of this type (Amchislavski, 1942) By bacteriological standards, lice are fairly easy to kill by heat, for the most resistant stage (the egg) is destroyed by 5 minutes at 55° C or 45 minutes at 50° C (Buxton, 1940c) However, the penetration of heat through thick garments is slow, and the method is unreliable unless rather a long exposure is used In practice it is necessary to hang up garments in a room with an air-temperature of 70° C for an hour (Busvine, 1944b)

Moving hot air is much more efficient in heating fabrics than still air, also it prevents the hot air from accumulating at the top of the chamber Early in the war a portable disinfectant with an air circulatory system was designed for the army, which disinfests a large load of clothes or bedding in half an hour (Richmond, 1940) The civil authorities, no less than the army, were alive to the greater efficiency of circulating hot-air disinfectors, and some very large plants were built to disinfest bedding from air-raid shelters (*Municipal Engineering*, 1945)

Fumigation

In the epidemics in eastern Europe after the 1914-18 war, the fumigant most commonly used for delousing was hydrogen cyanide This is, indeed, a highly toxic gas with good penetrating powers It has been used extensively for house-fumigation against bed-bugs in recent years, and the same procedure has been shown to be effective for destroying lice in a building (e.g. after removal of a typhus patient) (Busvine, 1943a) But, for the general delousing of clothing, cyanide is very dangerous, owing to the readiness with which it is absorbed by fabric and subsequently driven off by the warmth of the body Therefore, a number of other possible fumigants have been examined for effectiveness and freedom from residue (David, 1944a, 1944b) Some new substances have been recommended which can safely be used for disinfesting garments methyl allyl chloride and ethyl formate in England (David, 1943), methyl bromide in America (Latta & Yeomans, 1943), methyl formate in Russia (Evreinova, Pozin, Sobolev, Tregubov, Khovanskaya & Fedder, 1942) and trichloroacetonitrile in Germany (Rose, 1943) Simple methods were developed for use in the field, clothing is put into a metal bin or a reasonably gas-proof bag and sprinkled with liquid fumigant It was found that solid fumigants such as naphthalene and paradichlorobenzene were too slow in action to be effective by this method; they required very long exposures (over 24 hours) to destroy lice and nits (Busvine, 1943a)

Low Temperature

Insects are generally rather resistant to low temperature, so that disinfestation by refrigeration is scarcely ever considered feasible However, epidemics of louse borne typhus are quite liable to occur in parts of Europe and Asia where the outdoor winter temperature at night drops to very low levels Accordingly, the possibility of utilizing these natural low temperatures for delousing was investigated (Busvine, 1944b) It was found that exposure overnight to a temperature of -15° C or lower could be relied upon to destroy all lice and nits even in a thick fur garment

The Use of Insecticides

The measures described so far are adequate for destroying lice in garments but they give no protection from re-infestation During the war of 1914-18 troops of all the belligerents became and remained chronically lousy, in spite of widespread use of hot-air disinfectors and fumigation plants The foci of infestation were in the fighting line, remote from the field laundries and delousing stations Men newly arrived were soon infested from billets, dug-outs, or from their lousy comrades

Very early in the recent European war it was realized that some chemical treatment was required which would persist in the underwear and give protection from lice for as long as possible In general, two methods were favoured (a) a finely-ground powder-insecticide, which would cling in the fabric, protect for as many days as possible, and then could be reapplied by the individual soldier, (b) a method of impregnating the underwear so that it would remain toxic to lice for several weeks Work on these two lines was started in various countries independently, but later in the war there was the fullest interchange of information on the results of research in Britain, America and Russia

a Anti-lice powders. The original method of using a powder-insecticide against lice was to rub the dust over the inner surface of the undergarments with particular attention to the seams About an ounce [about 28 g] of powder was required to treat a man When more powerful insecticides became available, it was found sufficient to blow the dust up the arms, down the neck, and under the trousers or skirt, without undressing the infested person The whole process could be done in about two minutes, which was a most valuable economy of time, since it enabled huge numbers of civilians to be deloused within a short period. During the height of the Naples epidemic, about forty delousing stations set up by the American Typhus Commission treated a maximum of 70,000 people in a single day The simplicity and general applicability of the method to all members of the community contributed greatly to the successful quelling of the epidemic.

The earliest efficient powder-insecticide to be used against lice was the British "AL 63" formula, of which the principal active ingredients were derris and naphthalene (Craufurd-Benson & MacLeod, 1946) This was evolved early in 1940 and was widely distributed to the Armed Forces and to medical aid-posts in air-raid shelters In Russia, a dust containing diphenylamine was prepared and used in the same way In Moscow, in the winters of 1941 and 1942, two large hotels were commandeered, the staffs instructed on methods of treatment, and infested people were sent to them to be treated (Fedder, 1942) Another Russian dust of this type which gave very good results was the "SK" formula, of which the active principle was chlorinated turpentine (Ivanova, 1942, Khanenia & Juravlev, 1944, Soboleva, 1944)

When the Americans entered the war, they set several large teams of biologists, chemists, and medical men to study delousing methods The anti-lice dust first adopted for the U.S. Army was the so-called "MYL" formula, a mixture of pyrethrum, isobutyl undecyleneamide and dimethyl anisole (Soap, 1942, Davis & Wheeler, 1944) This was a very good insecticide, but the inclusion of the pyrethrum was a disadvantage, because all the available supplies of that material were urgently needed for other purposes

All the anti-lice dusts which have been described were superseded when DDT became known to the Allied Nations Originally a Swiss discovery, DDT has been the subject of intensive researches in Britain and America, which have extended its uses, defined possible hazards and improved the methods of manufacture (For a full account of this new insecticide, see Buxton, 1945) For use against lice in powder form, DDT is used at 10 per cent in any inert

mineral dust An ounce of this dust rubbed into the underwear prevents infestation by lice for 2-3 weeks (Bushland, McAlister, Jones & Culpepper, 1945)

The use of DDT dust applied beneath the clothing of dressed people with a hand dusting-gun has become the standard method of treating large numbers of infested people. It has been used with success in bombed cities and on refugees and prisoners of war, and has become the principal weapon for attacking a typhus epidemic

b Impregnated clothing The use of impregnated underwear against lice fulfils a different role from that of a powder. Impregnation is feasible only for people in uniform who can be issued with treated underwear and their discarded sets cleaned and re-treated. It is, therefore, a means of protecting soldiers and medical personnel from infestation for relatively long periods spent in areas where infestation is common

One of the first treatments which gave protection from reinfestation for about a month was the thiocyanate applications developed in this country in 1940-42 (Busvine, 1945). A similar idea was developed independently in Russia, where bis-ethyl xanthogen was used for impregnating underwear (Soboleva, 1942, 1944, Juravlev, 1944). In America the same line was followed in the use of strong pyrethrum preparations to treat sets of underwear (Jones *et al*, 1944). Some tests of pyrethrum-impregnation were also made in Russia (Kalabukhov, 1943). But all these processes suffered from more or less serious disadvantages. The thiocyanates were liable on occasions to produce smarting of the skin, bis-ethyl xanthogen has a strong unpleasant smell, pyrethrum is effective only at high rates which are scarcely practical, and all three are, to a large extent, removed by laundering

Once again DDT superseded all the other compounds for this particular use. Its advantages are that it is imperceptible to the wearer, it is entirely harmless in this form, very little is removed by ordinary washing and it persists for about six weeks before re-treatment is necessary (Jones, Fluno & Hendrick, 1945, Musgrave, 1946). Large numbers of DDT-treated shirts were prepared for the Allied armies before D-day, with the result that during the subsequent campaigns the troops were virtually free from lice. This was the first time that troops in active warfare under difficult conditions had been protected from general lousiness

B NEW WORK ON THE HEAD-LOUSE PROBLEM

Statistical Information

We owe a great deal of our knowledge of the bionomics of head-lice to the studies by Buxton in recent years (1936, 1937, 1938a, 1938b, 1940a, 1940b, 1941). These papers describe the populations of lice found in crops of hair taken from the occupants of hospitals and jails, mostly in Africa and India, but including men of several races. Irrespective of locality or race, the general trends were consistent, and later Mellanby (1942a) and Le Noury (1945) showed that they held good in Britain. Very briefly, the conclusions were these: there is a strong positive correlation between weight of hair (which is the best measure we have of length of hair) and infestation. On account of their generally longer hair, women and girls are more liable to infestation than men and boys. There is a negative correlation with age, children being more infested than adolescents, who are more infested than adults. The heaviest rates of infestation are to be found in groups showing the highest proportion of infested people.

Mellanby (1941) tried to obtain an estimate of the general level of head-lice infestation in Britain, taking as a reasonably unbiased sample records of examinations on entry into fever hospitals. The results (based on pre-war years) were very disturbing, for it appeared that nearly 50% of girls of school age and 30-40% of boys showed evidence of infestation. These figures were for urban districts, children in rural areas were much less badly infested. A later survey (Mellanby, 1943) showed that the situation was not much changed after four years of war.

Comparing the proportions of children infested in families of different size, it was found that the percentage increased with the number in family (Mellanby 1942b). An examination of the figures for recruits to one of the Women's Services revealed that infestation was most common among less-intelligent groups, as shown by intelligence tests (Rollin,

1943). These two accounts illustrate the association of head-lice infestation with poverty and ignorance

Advances in Control Methods

In a review of methods of controlling the louse, Buxton (1940d) describes the standard method for treating pediculosis capitis. The most usual methods were shortening the hair if possible, and combing thoroughly with a fine-toothed metal comb, or the application of paraffin, phenol, cresol or sassafras oil. All these methods, which were in vogue up to the beginning of the war, suffered from some disadvantage, they were either tediously slow, or else they were liable to be inefficient, none of them conferred any degree of protection from re-infestation.

The general mobilization and the evacuations of towns during the war were accompanied by more frequent medical inspections of our population. Among other things, much more attention was paid to methods of eradicating head-lice. The RAMC doctors, responsible for disinfection of large numbers of recruits, called for a treatment that was *rapid* as well as being efficient. Industrial medical officers, who had to deal with factory girls, needed some treatment which would not be resented by the patients. But, above all, there was the perennial difficulty of the school medical officer and the medical officer of health which can be summed up in one word: re-infestation. The common focus of infestation is the family group. In a recent American drive against pediculosis (Murphy, 1943), the home contacts of infested children were urged to come for inspection. Nearly 50% of them came and, of these, 80% were found to be lousy.

In order to overcome some of the deficiencies of the older methods of treatment, there have been a number of proposals for utilizing modern powerful insecticides against the head-lice. Busvine & Buxton (1942) tried out in clinical tests two different thiocyanates diluted in oil and rotenone made up in a cream and in a lotion. The advantage of preparing the drugs in this way was that they could be simply applied in the manner of an ordinary hair-dressing. Being hardly noticeable, they were not resented by the patient, and so would be left undisturbed for a week as a protection against re-infestation. These substances were widely tested (on some 10,000 heads) under the auspices of the Ministry of Health, and one of the thiocyanate formulae, the lethane-special hair oil, was recommended for general use (Ministry of Health, 1943, Busvine, 1943b). The same preparations and, in addition, pyrethrum were successfully used at somewhat lower dilutions in Canada (Twinn & MacNay, 1943).

The use of derris dust as a powder-dressing has sometimes been advocated (Buxton, 1940d, Murphy, 1943). But it is not effective unless the dust is left on the head for several days, which is usually resented by the patient, for it gives a chalky powdered effect to the hair. A way of employing derris which seems more promising is in the form of a shampoo (Trembley, 1943).

Benzyl benzoate emulsion, as used for the treatment of scabies, has some value in the treatment of pediculosis (Blackstock, 1944), though it is not perhaps as efficient as originally claimed. Certainly the compound has no solvent action on lice or nits (Smith, 1944).

According to the results of American work, an effective lotion can be made up with phenyl cellosolve (Davis, 1943, Hansens, 1945). The cellosolves are commonly employed as bases in perfumery, so that they are almost certainly harmless, phenyl cellosolve, however, is rather like glycerine and might give a slightly sticky appearance to the hair. The material appears to remain effective in the hair for about 4 days. Another lotion, recommended by other American workers, contains isobornyl thiocyanate as its active ingredient (Shelanski, Smyth, Clark, Zeller, Pious, Frank & Kramer, 1945). Like the phenyl cellosolve it is said to be easy to apply, and it leaves no grease, stain or odour, but as it is washed off on the day after treatment, it can have no protective effect.

In India, Roy & Ghosh (1942, 1944) claim to have obtained very satisfactory results by spraying infested heads with preparations of pyrethrum in kerosene.

Recently a number of these new anti louse treatments were re-examined and compared with the older methods by Scobbie (1945). Among the interesting results of laboratory tests was the high ovicidal action of phenol and lysol, also noted by Gamlin (1943). Scobbie tested the new insecticide DDT in the form of an emulsion, and her general conclusions were

that DDT emulsion and lethane-special oil stood out as the two insecticides of value in the treatment of pediculosis capitis. DDT was preferable to lethane, because one treatment with it secured a cure in every case, and because the period of protection after DDT treatment was 14 to 18 days as opposed to 4 to 6 days with lethane.

DDT treatment appears to be very promising, but it would seem desirable for results to be confirmed by larger trials.

C CONTROL OF CRAB-LICE

Some of the materials used for treating pediculosis have also been employed against the crab-louse, *Phthirus pubis*. Owing to the sensitivity of the skin of the genital region, caution must be exercised to avoid dermatitis. Twinn & MacNay (1943) used ointments and lotions containing thiocyanates, rotenone, or pyrethrum. The results were good,

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but the thiocyanates and rotenone were rather liable to cause superficial dermatitis, especially if the parts had been previously scrubbed, washed or shaved. Mellanby (1944) reported complete cures of 177 cases after a single treatment of an emulsion of lauryl thiocyanate. Roy & Ghosh (1944) advise shaving the affected parts in all cases and then spraying them with pyrethrum in kerosene. For phthiriasis of the eyelids, they advocate several treatments with pyrethrum ointment. Shelanski *et al* (1945) successfully treated 278 cases with two applications of their isobornyl thiocyanate emulsion.

Eddy (1944) suggests a three-purpose lotion for use against head-lice, crab-lice and scabies. It contains benzyl benzoate, pyrethrum plus an "activator," and dinitroanisole. (The benzyl benzoate is included for scabies while the rest of the ingredients occur in the MYL-formula anti-louse powder.)

RECENT WORK ON MOSQUITO CONTROL

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The object of any programme of mosquito control is the prevention of either disease or nuisance caused by the bites of mosquitoes. These objects can be secured in a number of ways, and in considering which to adopt there is one important difference to remember between the elimination of nuisance and of disease, in the former it is necessary to eliminate bites of all species of mosquitoes, in the latter the only essential is that bites by infected, and therefore relatively old, members of a limited number of species should be avoided. Whichever is the intention, however, the policy to be adopted will depend on the extent of the damage done and the economic resources available to counter it, the habits of the mosquito in selection of breeding places and shelters and in biting, the nature of the population to be protected,

whether dense or scattered, static or nomadic, and the characteristics of the countryside.

Several choices must be made between total eradication over large geographical areas and limitation of numbers to such an extent that disease or nuisance disappears—a method which does not exclude local eradication by permanent works where the land is suitable, between control of all mosquitoes and control of certain important species only, between attack on the aquatic stages and on the adult stage, between direct attack on the mosquito, and protection of the individual as by screening or repellents. These are decisions of policy, slowly influenced by the growth of knowledge and experience, which must be made before a programme of mosquito control is started. Subordinate to them are decisions on technique,

which undergoes continuous rapid change without materially affecting the general principles of work

POLICY OF MOSQUITO CONTROL

1 Eradication or Control?

Control of mosquitoes, or the reduction of numbers to such an extent that they cease to cause nuisance or disease, was the generally accepted policy until the continued existence of "seed beds" of yellow fever in five or six areas of South and Central America, despite control measures on the usual lines, brought into being the Brazilian organization described by Soper (1937) for the eradication of *Aedes aegypti* from those districts. The essentials of the organization were first, a strong legislative support which gave full rights of entry and protection of workers, and, secondly, larval control by anti-larval gangs, supplemented by adult-catching gangs which sought for adult mosquitoes in areas from which larvae were thought to be eliminated, and mother-focus gangs which spared no effort to find and eradicate residual breeding places whose existence was made apparent by the continued existence of adults in places where complete larval destruction had been assumed. Success was complete, once an area had been declared free of *Aedes*, anti-larval work could be abandoned, and the sole work needed was an occasional check by adult-catching gangs to make sure that re-invasion had not occurred. The "seed beds" of yellow fever disappeared, and epidemic urban yellow fever ceased to be the constant plague of South America that it had been for hundreds of years.

In 1931 *Anopheles gambiae* entered Brazil from West Africa. By 1938 it had invaded an area of about 5,000 square miles [about 1,300,000 hectares] extent and caused devastating epidemics of malaria. Instead of control, the principles of eradication developed for the prevention of yellow fever were applied by Soper & Wilson (1943) at the beginning of 1939. Legislative support, an ample staff, division of the infested area into divisions, posts, districts, and zones, each with its own trained staff, simplification of work so that each man had to know and use one technique only—but know and use it well, the application of hand-strewn Paris green to all water surfaces once every week, adult-catching to check the results of anti-larval work, careful search for residual breeding places when adults were found, and most careful organization and delegation of work, resulted in the eradication of *Anopheles gambiae* from Brazil in 19 months. Work was continued for some time to ensure freedom, after which nothing more than a quarantine service to prevent re-entry was needed. The total cost of the work was \$2,139,570, insignificant when compared with the danger to which the country had been exposed, or to the capitalized cost of continuous control on the old lines.

The demonstration of this possibility overshadows all other developments in mosquito control. The decision to attempt eradication can be made only by Governments, but where it is possible the advantage to be gained is so great that it should be seriously considered in all countries affected by mosquito-borne disease. The decision has already been made by the Egyptian Government, and an effort is now being made to eradicate *Anopheles gambiae* from the Nile Valley, which it infests as far north as Assiut.

Success depends on the existence of barriers to re-entry, on the habits of the mosquito, on the climate, on the terrain, and on the intensity of the effort at eradication, it is clearly possible in island territories where the same mosquito carries disease, such as Mauritius, it is probably possible in islands infested with other species, such as Sardinia, Sicily, Crete, Cyprus, Ceylon, or the West Indian Islands, it may be possible in mainland territories where existing natural barriers can be artificially improved to make a secure protection against re-invasion.

2. General or Species Control?

As early as 1902 Stephens and Christophers pointed out the exclusive role of certain mosquito species in the transmission of malaria, and the consequent advantage of concentrating on their control. Through the work of Watson and of Ramsay, this principle has become generally adopted in India and the East, where as a rule the disease-carrying mosquitoes are in a small minority, and have well-defined preferences in the choice of breeding places. In Europe and Africa they represent a higher proportion of the total and have less well defined preferences, also there is a need to

prevent yellow fever and dengue as well as malaria, and as a result, where mosquito control has been practised, it has usually been general mosquito control.

The differentiation of *Anopheles sacharovi* and of the various races of *Anopheles maculipennis*, the demonstration of their varying importance in the transmission of disease by Hackett & Missiroli (1935), together with the definition of preferences in choice of breeding places, made concentration on important species an efficient and economical method in Southern Europe.

Now the differentiation of *Anopheles melas* from *Anopheles gambiae* by Ribbands (1944a), the demonstration of the special and highly localized nature of its breeding places by the same author (1944b), and of its supreme importance in the transmission of malaria, have brought into prominence the advantages to be gained from concentration on important species in Africa. As our entomological knowledge increases, so will our ability to define exactly the breeding places of disease-carrying mosquitoes, and corresponding emphasis will be laid on the value of species control.

General mosquito control should be attempted wherever the human population is dense, as in urban areas, and the expense of nuisance control is not disproportionate to the means of the people benefiting from it, and wherever disease-carrying mosquitoes form a majority of the total, or are to be found breeding in most types of surface water, though these areas are likely to decrease as our knowledge increases.

Species control is indicated particularly where the scattered nature of a population makes the burden of general control excessive, and only a small proportion of the surface water is selected as breeding places by disease carriers.

3 Attack on Aquatic Stages or Adult Stage?

Attack on adult mosquitoes, to the exclusion of attack on the aquatic stages, had not been thought to be a practical measure of disease prevention until the evidence of Ross (1936) and de Meillon (1936) proved that adult destruction alone, by spraying of houses periodically with a pyrethrum spray, could reduce the incidence of malaria at a cost below that of larval control under certain rural conditions. This was rapidly confirmed by Covell, Mulligan & Afridi (1938) in India, it became the subject of a prolonged study by Russell & Krupe (1939, 1940, 1941) and the same authors with Sitapathy (1943) in an area of South India with a high malaria prevalence due to transmission by *Anopheles culicifacies*, and it has been brought into extensive use in Army practice.

Russell and his co-workers recorded some decrease in the general density of anophelines following spraying twice weekly, without any definite change in larval density, but with a very marked reduction in malaria as measured by spleen- and parasite-rates, a result attributed to a reduction in the average length of life of the mosquito, most being killed before they had become infective. In confirmation of this explanation, sporozoite-rates are usually found to be greatly decreased in sprayed areas, though the percentage of mosquitoes containing human blood remains unchanged. The extent of the reduction secured and the cost of work is shown in Table I.

TABLE I
CHANGE IN THE SPLEEN RATE FOLLOWING SPRAYING OF HOUSES TWICE WEEKLY
(Modified from Russell, Krupe & Sitapathy (1943))

Village	Seasons Sprayed	Spleen-rate		Cost per head per annum.
		Before	After	
		%	%	Pence
Kasangadu	1938, 39, 40	57.1	Nil	6.5
Attikottai	1939, 40, 41	15.0	1.3	6.6
Modalchen	1940, 41	71.4	1.6	5.5
Perumalkovil	1940, 41	40.5	14.1	8.25
Sandakottai				
Pallinkondan	1941	45.0	10.8	3.4
Tamamakottai				
Palavankadu	1941	42.5	9.6	8.4

Personal experience in the Mediterranean basin, and other evidence, confirms this finding that the object of disease prevention but not of nuisance prevention can be achieved by this means, at astonishingly low costs, by a method having the advantages of securing speedy practical results in the presence of an epidemic, and of lack of dependence on the complexity, or difficulty of identifying, the important mosquito breeding places. It appears to be the ideal method for emergency use after outbreak of an epidemic of mosquito-borne disease, and for scattered populations whose resources are unequal to the cost of larval mosquito control.

4. Attack on the Mosquito or Protection of the Individual?

Protection of the individual as a first line of defence has never been relied on except where mosquito control has been practically out of the question, owing to its disproportionate cost to the economic status of the community, usually scattered and rare, or to the nomadic nature of the community which makes foresight in control impossible, a marked characteristic of forward troops. Developments in repellents have now made individual protection a completely practical proposition. The use of nets, and of screened quarters, remains an invaluable second line of defence for all.

TECHNIQUE OF MOSQUITO CONTROL

1. Measures directed against Adult Mosquitoes

a Insecticidal agents The serious shortage of pyrethrum early in the war made necessary an extensive search for other equally, or more, effective insecticides. Many were tried, lethane 384, lethane 384 special, thanite, and others were found effective, but none was as effective as pyrethrum for its immediate insecticidal effect, though DDT and gammexane, referred to below, were found to have far superior properties as residual insecticides. It was, however, shown that the efficacy of pyrethrum sprays can be increased by the addition of certain oils, notably sesame oil, to the solvent, which act by altering the physical character of the droplets produced in the spray. As a result it has become common to add 2% to 5% of sesame oil to sprays, an addition which makes it possible to reduce the pyrethrum content from 0.1% to 0.07% without lessening the efficiency of the product. Also it was found that the addition of pyrethrum to other sprays with a less-immediate action increased their activity, by virtue of the irritant effect of the pyrethrum on mosquitoes, which causes them to leave shelters and expose themselves to the cloud. In consequence it is common practice to add 0.03% pyrethrins to DDT sprays (usually 0.5% DDT) to increase their activity. These three sprays are roughly equal in potency, and in each case the required dose is about one ounce to 3,000 cubic feet, or 0.33 cm³ per cubic metre, of air.

DDT, or 2,2-bis(4-chlorophenyl)-1,1,1-trichloroethane, and later gammexane, or the gamma isomer of benzene hexachloride, were found to be potent residual insecticides, treatment with which renders surfaces lethal to mosquitoes and other arthropods for long periods of time. The properties of DDT have been fully reviewed by Buxton (1945), knowledge of the properties of gammexane is less advanced, but has been reviewed by Slade (1945). The best effects with DDT have been secured by the use of oil solutions, though oil-water emulsions seem equally promising as vehicles. The usual solution has been 5% in a medium oil, applied at a dose of 100 mg DDT per square foot (roughly 1.0 gram per square metre). The duration of the lethal effect under field conditions has not yet been fully studied, but an effective period of 8 weeks as a minimum has been reported, during which time the mosquito population was reduced to one-fifth of its previous density. However, much work remains to be done on this and allied subjects, for example, the dosage needed on different wall-surfaces such as thatch and rough plaster. Trials against other arthropods suggest that gammexane should be as effective as DDT for this purpose, though small-scale trials by Craufurd-Benson (personal communication) in Italy indicated that there was a marked repellent effect, probably due to other odorous isomers, which deterred mosquitoes from landing on treated surfaces and receiving a lethal dose.

b Methods of application. Trials have been made of the application of pyrethrum, DDT, and gammexane in dust form. Pyrethrum was reported to have a prolonged repellent effect in this form by Garnham & Harper (1944), but unpub-

lished experiments by the writer in Palestine were less successful, probably due to the lower atmospheric humidity in that country. DDT and gammexane have a similar effect as dusts to that in oil solutions, but probably less prolonged, and the method is therefore of less value.

Other trials have been on emulsions in water or oil solutions, with the object of saving much of the cost of the vehicle. This method of applying DDT is probably as effective as the use of oil solutions, but pyrethrum is rapidly destroyed by hydrolysis and the method is of use only in large-scale work where immediate use of the emulsion can be assured. Where this is the case, a marked reduction in costs results without loss of efficiency. Russell, Knipe & Rao (1942) emulsify one gallon of stock pyrethrum extract (presumably containing about 1.0% pyrethrins) in seven gallons [about 32 l.] of water, using 184 grams of sodium lauryl sulphate as an emulsifying agent, and thereby reduce the final cost of a dilute spray made from flowers from 25.5 pence to 8.7 pence per gallon. When used fresh, the emulsion is as effective as an oil solution, and the effect of this economy on the overall cost of adult control is shown in Table I, for the village of Sandakottai. Pallinkondan was the only one in the series in which the emulsions were used, oil solutions being used in the others.

The ordinary hand-spray has proved too fragile, and too wasteful of time and labour, for anything except very small scale domestic work. Various improved types of hand guns have been developed, and descriptions of good types have been given by Knipe & Sitapathy (1942), but the tendency has been to use apparatus using higher air-pressures of the order of 15 pounds per square inch [about 1.05 kg per cm²], developed either by manual pumps separate from the spray-gun, or from power compressors, or from compressed gases. A description of the first type is given by Russell, Knipe & Sitapathy (1943), who operated their spray-guns through pressure-reducing valves from portable air-tanks, filled to 90 pounds per square inch air by either manual or power compressors, and found this the best, most economical and reliable method at their disposal.

Spray-guns operated direct from power compressors have been widely used in the army, where they have proved very effective though less economical than the previous method, and a good description was published by Wats & Bharucha (1940), who used either electrical or petrol-driven apparatus supplying 3 cubic feet [about 0.085 m³] of air per minute at 30–35 pounds per square inch pressure. Examples of the last type are the freon-pyrethrum aerosol described by Russell (1943) and widely used with great success in American Army practice, an apparatus using solidified CO₂ described by Knipe (1941), and one resembling a miniature soda-water siphon worked by compressed CO₂ in a small capsule or "Sparklet" used with success by Mackie & Crabtree (1938) in disinfecting aircraft. Each of these types of apparatus has its own sphere of utility, a good hand-apparatus is most suitable for work in rural areas where skilled mechanics are not available and the average village is small in size, power-driven apparatus, particularly when several portable air-tanks are used, is invaluable in larger villages and towns where mechanics can be secured, the freon type has proved of very great value in the protection of American troops, but in the opinion of the writer should give place on grounds of economy with equal efficiency to the last-mentioned type, used with concentrated insecticides of about 1.0% pyrethrum content for small-scale use under static postwar conditions.

However, progress will not necessarily be through the development of sprayers alone, success has already been achieved with insecticides distributed in smokes, as by Pogodina & Sokolov (1940), a medium very suitable for distribution of DDT, while the immediate and residual lethal effect on adult mosquitoes of fine sprays of DDT solutions distributed from aircraft is already attracting attention. Those types of apparatus which produce a mist, or aerosol, are not the most satisfactory for the distribution of residual sprays, in the application of which a wetting spray is needed. The best yet available in the writer's opinion is a knapsack, hand-operated, pressure-sprayer, in which fluid is pumped direct to a simple nozzle of the humidifying type and of $\frac{3}{16}$ inch [about 0.8 mm] diameter.

2. Measures directed against the Aquatic Stages

Measures against the aquatic stages may consist in the prevention of man-made breeding places, the modification of breeding places by mechanical or naturalistic means, the

eradication of breeding places, or the direct destruction of ova, larvae and pupae

a Mechanical The importance of the prevention of man-made breeding places has been shown vividly by Russell (1938) in his description of the increase in malaria following minor engineering aberrations when irrigation was introduced into the Cauvery district of South India, and not as a necessary result of the provision of adequate water for irrigation of the land. Work on modification of breeding places is chiefly notable for the development of the use of fluctuating water-levels in reservoirs, rice fields, and in streams, by sluicing. The biological mechanism of this method has been reviewed by Hinman (1938), the application to rice-fields by Hill & Cambournac (1941), and siphons for automatic sluicing have been described by Macdonald (1939), Ramsay & Anderson (1940) and others

Thomson (1942) has summarized his researches on the mechanism of the naturalistic control of *Anopheles minimus*, after the general subject of naturalistic control had been exhaustively surveyed by Hackett, Russell, Scharff & White (1938), and methods of drainage of brackish coastal swamps, long used in the control of *Anopheles sundatus* in the East, have been adapted to the control of breeding places of *Anopheles melas* and fully described by Gilroy & Chwatt (1945), but the main new work has been on the direct destruction of the larval form by chemical means

b Chemical The importance of the introduction of paris green dust was matched by the development of paris green suspensions in kerosene/water emulsions, by Barber, Rice & Mandekos (1936), and the simplification and improvement of the method by Aziz (1939) to a plain suspension of paris green in water, a method of which the writer has much experience in the control of *Anopheles superpictus* in eastern Mediterranean countries. A 1/500 suspension of paris green in water, made on site, is sprayed on water in such a way as to give a final dilution of about one part paris green in one million parts of water (i.e. one gallon to 1,200 square feet [11 to 25 m²] of water 3 inches [7.6 cm] deep), and kills anopheline and culicine larvae in both standing and moving water. The absence of any weighty material for transport, the ease of application, and the efficacy in moving water, makes it ideally suited to the treatment of small streams in mountainous country, where paris green in the dust form is useless, and oil presents often an excessive transport problem.

The second, and ultimately but not immediately more important, advance has been the discovery of DDT, the applications of which have been reviewed by Buxton (1945). It has usually been applied in the form of a 5% solution in a medium gas- or diesel-oil, often with the addition of a spread-aider such as 0.5% oleic or cresylic acid, in which form a dose of 5 mg per square yard (0.8 ounces per acre, or 50 g per hectare) gives a 100% kill of larvae provided distribution has been even, though practical difficulties necessitate the use of somewhat larger doses of the order of 4 ounces to the acre. The main difficulty in securing the full larvicidal value of this substance has been the defects of our distribution apparatus, which is mostly adapted to the spread of much larger quantities, and this apparatus must be developed to correspond with the qualities of the larvicide used in it. In war, extensive and very successful use has been made of aircraft, a method probably too expensive for all except very large undertakings in peacetime. The tendency will probably be to the development of smokes, of oil solutions with very high spreading powers, and of simple apparatus of the drop-bottle type.

A search for substitutes for paris green was precipitated by local shortages during the war, and as a means towards economy. Copper cyanide is certainly an adequate substitute, either for the dust- or the water-method of distribution, and

is effective in somewhat smaller doses than paris green. Hinman, Crowell & Hurlbut (1942) strongly recommend the use of copper arsenite, a cheaper and equally effective substance, and calcium arsenite has been favourably reported on. The tendency towards the use of pyrethrum solutions has been checked by wartime shortage, but not until it had showed distinct promise as a means of greatly increasing the toxicity of oils, and had presented some curious problems described by Chopra, Roy & Ghosh (1940) who came to the conclusion that the toxic effect did not run parallel to the pyrethrin content. Phenothiazine, paradichlorobenzene, tetrahydronaphthalene, and other substances have been proved efficient larvicides, but when shortages of supply of the more usual larvicides end, all will probably disappear except perhaps phenothiazine, which is effective in a dose of 7 to 14 ounces per acre [0.5-1 kg per hectare].

3 Prevention of Bites on Man

a Mechanical Protection Davey & Gordon (1938) have defined the requirements of screencloth to exclude West African mosquitoes, concluding that the aperture should not exceed 0.047 inch [about 1.2 mm] which represents screencloth of 16 × 16 mesh made of 28 SWG¹ wire, though other combinations of mesh and gauge will secure the same result, and screencloths made of plastic, which will probably be free from many of the disadvantages of metal cloths, have been introduced, but there has been little other development in mechanical protection.

b Repellents Study of repellents has been greatly encouraged, in the hopes of finding a more efficient substance than citronella oil for the protection of mobile troops during the war. Granett (1940) reviewed the test-procedure for evaluating repellents, giving full bibliography, and concluded that at that time the best repellent was a proprietary preparation containing diethylene glycol monobutyl ether acetate and diethylene glycol monethyl ether, though this has since fallen into disuse owing to possible toxic properties. Dimethyl phthalate has since become recognized as a pre-eminent repellent, giving full protection for 6 or more hours when applied to the skin as a thin film, except where mechanical removal, by sweating or friction of the hat-band, or actual handling of the face, occurs, when the effective protection may die off in 1-2 hours. It is free from irritant, or other objectionable effect except when it comes into contact with the eyes or mucous membranes, and apart from this minor disadvantage is an ideal repellent which has at last made the protection of individuals possible where no other means of mosquito control can be practised.

CONCLUSION

Recent work has emphasized the possibility and advantages of eradication of mosquito species, at least under certain conditions, in place of the continuous control previously practised. It has also emphasized the value of adult mosquito control, particularly for the protection of scattered rural populations, and species control is growing in importance. Technique has improved by the further development of methods of destruction of adult mosquitoes, and particularly by the use of DDT as a residual insecticide, by the improvement of methods of larval destruction, particularly water-borne paris green and later DDT solutions, and by the discovery of efficient repellents which make individual protection a possibility. With these advances there is now no problem of disease or nuisance caused by mosquitoes which cannot be overcome, and almost always at a cost commensurate with the advantages to be gained.

¹ [Standard wire gauge. No 28 SWG represents wire 0.014 in (0.376 mm.) in diameter]

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INSECT REPELLENTS

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Substances of various kinds to protect plants against insect pests have long been used in agriculture. Much less attention, until recently, has been devoted to substances to destroy or protect against insect pests that attack man. During the war, however, the necessity of affording protection to our troops against diseases transmitted by various forms of biting insects led to an enormous amount of work being done, most of it still "restricted" and not yet available for publication, directed to the discovery of new effective insecticides and protective substances, and methods of using these.

The subject has thus come to cover a very large field, and it is perhaps well to start by stating what is meant by a repellent. Substances used to kill insects for whatever purpose are termed "insecticides." These may be used in liquid form sprayed on insects such as flies or mosquitoes as "insecticidal sprays," or "aerosols" if the spray particles are very fine and mist-like, or sprayed on water to kill the larvae of mosquitoes as "larvicides," or used to impregnate or dust clothing to kill lice as "lousicides," and in many other ways. Substances burnt to act as smoke or vapour, to kill or drive away mosquitoes or other insects are "fumigants." "Repellents" are substances smeared on the skin, or used to impregnate clothing, to prevent or discourage mosquitoes or other insects from biting.

Repellents may be, but most commonly are not, insecticidal. They serve all the purpose asked of them if they prevent the insect from biting, and it is immaterial whether they kill the insect or not. Of these different kinds of substances we are concerned here only with repellents, what they are, how they act, how they are used, how they are tested, and what can be expected from them.

As most of these substances have been developed in the first instance against mosquitoes, and as more is known of their action in this respect than in any other, most of what is said in this article refers to repellents against mosquitoes. But for the most part this will apply with minor qualifications to all biting insects of this nature, such as midges, sandflies, jungle-mites, and even leeches which are so troublesome in tropical jungles. Also repellents, though one may be especially effective against some biting insects and another against others, as a rule are fairly general in their effect.

Early Work on Repellents

Fumigants and preparations smeared on the skin to drive away or prevent mosquitoes from biting have long been in use as more or less domestic remedies. Probably primitive man, as do some tribes at the present time, used smoke to ward off their attacks. One of the first to bring together what was known in this respect was Howard (1916). Among the best of these remedies he refers to spirits of camphor, oil of pennyroyal [*Oleum pulegi*] and oil of citronella. A mixture recommended is oil of citronella 1 ounce [28.5 cm³],

spirits of camphor 1 ounce, and oil of cedar $\frac{1}{2}$ ounce. A few drops on a bath-towel hung over the head of the bed, or a few drops on the face and hands, is said to prevent mosquitoes from troubling for some hours. There were also "smudges" (substances making smoke when burnt) and "fumigants." Of the latter, one example that may often be seen used by the housewife in India and probably in other tropical countries is little cones, or sometimes sticks (joss-sticks) or spirals, made from pyrethrum powder moulded and dried and allowed to smoulder after being lighted in a room to dispel the mosquitoes. Howard refers to *Datura stramonium* used in the same way with 1 part nitre to 8 parts of the powdered leaf. Mimm's culicide is another such fumigant given by Howard—equal parts of carbolic-acid crystals and gum camphor, the crystals melted and poured on the camphor, giving a clear, rather volatile fluid with an agreeable odour. 3 ounces are volatilized over a lamp per 1000 cubic feet [28.4 m³]. Sulphur, 2 pounds [0.9 kg] per 1000 cubic feet is another rather drastic fumigant.

All operations of this kind are now much more effectively carried out by spraying with "flit" or other knock-down insecticidal sprays, of which a number are on the market (these are most commonly used against flies, but are also effective against mosquitoes). Such spraying may be done with an ordinary domestic "flit-gun" or by various ingenious automatically-acting devices actuated by the small soda-water-charging capsules, or more powerful flit bombs are used professionally. Perhaps one of the most notorious of these old remedies, in this case used as a repellent for smearing on the skin, was Bamber oil (oil of citronella $1\frac{1}{2}$ parts, liquid paraffin 1 part, coconut-oil 2 parts, to which is added carbolic acid 1%). In fact, so far as repellent mixtures were concerned, oil of citronella in some form or another will almost invariably be found as the chief ingredient. Oil of citronella as a repellent is at present in disfavour owing to its temporary effect. But there is much to be said for it, as will be seen later.

In the decade 1920–30 we find for the first time actual research on repellents carried out on scientific lines by Bacot & Talbot (1919), Bunker & Hirschfelder (1925), Rudolfs (1924, 1930) and others. During this period large numbers—as it was then counted—of substances were examined and tested both in the laboratory and in the field. Among substances found most effective by these observers were oil of thyme, oil of cassia, spruce oil, oil of citronella, oil of lime, oil of turpentine, oil of tar (very effective in the Arctic, but too dirty for ordinary use). Some, such as oil of cloves, were effective but too irritating to the skin for practical use. All these it will be noticed are substances of the essential-oil type, a number of which even now, such as oil of cassia, give very good results up to some hours. Preparations of pyrethrum were at this time also experimented with and found effective.

But in spite of all the work done nothing very outstanding was found, protection lasting at most for a few hours. The only observers who appear to have attempted to find whether any particular feature in molecular structure was concerned in repellency were Bunker & Hirschfelder, who tested alcohols, aldehydes, ketones, ethers, esters and so on. They found the hydrocarbons strikingly ineffective, phenols were better but not impressive. Effectiveness seemed to enter with the O atom, especially with the COH of the alcohols, or the COO of the esters, or the CO of the ketones and aldehydes. It was very difficult they admit, with the methods in use, to assess the relative value as repellents of the substances tested. What was really fatal to most of these studies was that there was no really critical quantitative method of measuring repellent effect under standardized conditions, and that the volatile nature of most of the substances of this simple kind tested make it improbable that a really effective lasting repellent would be found. Possibly due to the rather disappointing results obtained by these workers, little further attention was given to the study of repellency until during the war.

War-time Developments

When the need for repellents to protect the Armed Forces as an antimalaria measure became vital, attention was naturally directed first to those substances which past experience had indicated as showing most promise, i.e., oil of citronella and pyrethrum. The demand for a repellent which would last all night, or in other words have an effective duration of at least six hours, soon excluded the first-mentioned substance.

Pyrethrum appeared to offer more hope of success. Owing to its extensive use in agriculture and its extraordinarily rapid lethal properties, an immense amount of work, chemical and otherwise, had been devoted to this substance. Its activity was known to be due to two complex chemical compounds, pyrethrins I and II, and, by means of estimating these, accurate quantitative work was possible. Extracts were available containing as much as 40% of these substances, and for a time the desired end seemed to lie in this direction. Pyrethrum, however, though a powerful insecticide in practice and in tests in the laboratory, gave relatively poor results as a repellent. Other lethal agents such as derms, nicotine—too poisonous for use as a repellent—and a new powerful insecticide "thamite" then on the market, were none of them satisfactory as repellents. Nor indeed, as later events showed, is DDT.

About this time, however, very extensive work on repellents was begun in the United States, especially at the Orlando Institute in Florida, at which Institute since then literally thousands of substances have been tested as repellents. The first result of this systematic work of testing was "Indalone," a proprietary chemical. This was followed shortly by the discovery of another very strong and lasting repellent commonly known as Rutger's 612, and after a further brief interval by that of still another compound, the now widely-used dimethyl phthalate.

Whilst these substances, especially the last-named, have now come into almost universal use, it must not be supposed that they are unique, for many substances having powerful repellent properties were discovered as a result of such testing. But it so happened that for one reason or another these were the most suitable for use. Unfortunately it is not possible, owing to war restrictions still in being, to go deeper into this subject, but mention of these now widely-known repellents will serve to give at least the main practical results achieved during this period.

Testing of Repellents

Two main forms of tests for repellency have been employed, (a) those performed in the laboratory, and (b) those carried out in the field. Field-tests, of course, approximate most nearly to the conditions under which the repellents are to be used, but they have the great disadvantage that conditions affecting the biting of mosquitoes are very variable and it is difficult to obtain satisfactory comparable results.

In the laboratory, the essential requirements are the use of rigidly standardized tests with mosquitoes of known species, numbers and age, reared and employed under identical conditions. The species of mosquito most usually employed for such purposes is *Aedes aegypti*, the common day-biting house-mosquito of the tropics. This species is eminently

adapted for laboratory work, being an active and non-temperamental biter and, if appropriately used, capable of giving reproducible results. Since, however, not all species of mosquito behave quite alike to any particular repellent, and since it is the anopheles mosquito against which protection in war-time is especially needed, tests are also made using some species or other of this genus.

The commonest method of evaluating repellency is to observe the time taken before the first bite takes place. A more satisfactory method is to expose the treated arm at fixed intervals, e.g., at 2, 4 and 6 hours, for some fixed period such as 15 minutes, by which time mosquitoes will have had plenty of time to decide whether or not they are going to bite. During the time of exposure, the number of mosquitoes, if any, settling on the arm is noted, and afterwards any wheals are counted and charted. From such data, by a sort of code arrived at by experience, a graded number or a graded series of signs can be used to assess the repellency as shown at each exposure. With dimethyl phthalate, using 100 female *Aedes* 5-7 days from emergence at 25° C and 90% relative humidity, 5 mm² per square inch [6.5 cm²] will just give complete protection for the treated arm for 6 hours.

Should a substance show exceptional repellent properties it has, of course, still to be considered whether it is sufficiently non-irritating to the skin, and not toxic by absorption and in other ways suitable for practical use.

Contact- and Distance-repellency

Repellents do not all behave exactly alike in their manner of exerting their repellency. The most marked difference in this respect is the extent to which any particular repellent acts at a distance or on contact. This can be tested in an appropriate apparatus, using a source of warmth as the attractor, and measuring repellency opposed to this. It is possible to do this quantitatively, and to give a figure for the degree of repellent effect at a distance. Almost all repellents show some effect at a distance, but in some, e.g., indalone, the figure representing this is very small. Dimethyl phthalate gives a figure of about +2. Oil of citronella gives one of +38-40. In fact oil of citronella will tend to drive mosquitoes away, so that Howard's reference to a few drops on a towel hung over the head of the bed, though perhaps a little optimistic, has some basis in fact.

How do Repellents Act?

Strictly the answer is that we do not know. It is not smell, or not necessarily so, or—to be cautious—it is not smell as perceived by ourselves, for many effective repellents have little or no smell, and with many that have some smell it is often neither pungent nor unpleasant to the human nose. That it is something very definite to the mosquito is shown by their behaviour. For when a mosquito from inadvertence or over-boldness alights on skin treated with an effective repellent, he leaves this so precipitately as to suggest to the observer a man who has accidentally touched a hot metal plate.

Some sense-organ must clearly be concerned, but whether the rebuff is given to sense-organs in the tarsi, especially the hind tarsi which *Aedes* seems to trail behind her as sensitive prospecting feelers, or whether the effect is exerted through the spiracles cannot at present be stated. Clearly this is a line of research which might yield much important information. It is a peculiar fact that many of the most effective modern repellents are of the class of substance known as plasticizers and used as solvents in the plastic industry. Whether this property of loosening the long molecules of which plastics are composed plays any part in repellency is again quite unknown.

Repellents and Repellent Preparations

Repellent compounds are usually of an oily nature and thus can be readily applied and spread on the skin. Such use of repellents is usually spoken of as 'straight' application. Whilst the straight method has many advantages it has also certain disadvantages, and many persons prefer some form of cream or other preparation containing the repellent. It is possible too that such preparations might help to retain the repellent longer on the skin. Much attention has been given to this question of a medium or vehicle. Such medium or vehicle may be paraffin or other waxes of suitable consistency, or various forms of cream.

There is no difficulty in making such preparations of any degree of elegance, but it is doubtful, except for aesthetic reasons, whether much is gained by doing so. At present the one almost insuperable difficulty in regard to repellents is that, however effective and durable a repellent may be, if left protected from rubbing on the skin its period of effectiveness will be grossly shortened if the treated area is rubbed by clothing or affected by profuse sweating. So far, except for certain efforts at a non-rubbable form of drying paste which for various reasons are unsatisfactory, the ideal of a preparation which will ensure lasting effectiveness for many hours in spite of rubbing by clothing seems as far off as ever. In general, then, the use of repellents in other form than the "straight" does not, except for aesthetic purposes, at present seem to offer much advantage.

Method of Using Repellents

We have seen that repellents may be either the liquid compound itself or some cream, paste, or other preparation containing the active ingredient. In either case the procedure for using it is much the same. It is usually recommended that about half a teaspoonful be shaken or poured into the palm of one hand or, in the case of a cream, that a suitable quantity of the material should be similarly taken and that, after bringing the two palms together, the repellent should be spread over the hands, exposed portions of the arms, face, neck and any other bare skin areas, more repellent being taken as required. It is best, however, if one can do so, to apply the material fractionally, since too wholesale a method is apt to leave more than is required where first applied and an insufficient amount where it is perhaps more required. Too great excess is unnecessary, but parts should be thoroughly smeared and "rubbing in" favours duration of effect.

A rather commonly-held idea is that a few wipes of the repellent are all that is necessary. This may be suitable for such a repellent as oil of citronella, and it is probably the rather common use of this repellent which has given rise to this belief. But with the modern long-duration repellents, untouched areas will not be protected and the mosquito, who prospects in her hunting very effectively, will have no difficulty in finding such spots. Thoroughness in covering all exposed areas is therefore very essential. A word of caution is perhaps desirable to avoid the neighbourhood of the eyes, as dimethyl phthalate on the tender skin in this region is apt to be unpleasantly irritating and especially so if it gets into the eyes. Common sense with experience will soon show what is best to do.

In such an article as the present there is a difficulty, for there are two rather conflicting issues underlying the use of repellents which it is perhaps well to have clearly stated. For military purposes the great desideratum has been to obtain a repellent which will be lasting and will not require renewal for, say, the whole night. It is this requirement which has eventuated in what has been here termed the modern repellent. On the other hand the civilian is usually not so concerned about duration. Protection for an hour or two may often be all that he requires, and if it is a matter of spending the night exposed to mosquitoes, then he can usually use

a mosquito-net, and should do so if he possibly can. For the civilian then, perhaps sitting of an evening in his garden, or fishing or shooting, a good oil of citronella might be his best choice. In this case it is only right that he should know that there are different grades of citronella oil, some being much adulterated. It should be a good Java oil, or better he might use the effective ingredient, citronellal, or the even stronger alcohol citronellol, either of which he may be able to obtain. On the other hand dimethyl phthalate is extremely effective and would certainly be worth trying.

Use of Repellents on Clothing

Since mosquitoes readily bite through most clothing when there is only a single layer over the skin, a great deal of attention has been given to impregnating fabrics with dimethyl phthalate. The remarkable feature here is the length of time, a week or longer, during which clothing so treated remains repellent. Nor is it necessary that this impregnation should be carried out in the orthodox fashion, for considerable protection may be obtained by smearing dimethyl phthalate with the hands over part of the clothing liable to be penetrated. Such methods, however, will probably have little application in civil life. In practice the experienced dweller in the tropics does not willingly expose himself in the evening in a single thickness of any part of his clothing, and protection against mosquitoes is far from being entirely or even mainly a matter of the use of repellents, but of suitable protective clothing such as mosquito boots, and having an undergarment beneath the trousers. Even for the civilian, however, a repellent may be a useful adjunct towards protection, since it will enable him to protect the neck and ears, which it is not easy to do with clothing.

What has been said about repellents may seem rather confusing and unsatisfactory. But the truth is that the simple idea of preventing mosquitoes from biting by smearing some substance on the skin is one that is most difficult in accomplishment, and one to which a really and completely satisfactory answer has not yet been achieved.

It will be clear from what has been said that much depends upon what exactly a repellent is desired to do, and the conditions in which it is to be used. The person sleeping in a temperate country, bothered by an occasional mosquito and desiring to avoid this nuisance, may still rely on some of the household remedies so graphically described by Howard. If not quite so optimistic as to put great faith in the few drops of oil of citronella on a towel placed over the head of the bed, there is still a good deal to be said for such simple remedies as the pyrethrum cone or joss-stick, which will undoubtedly, to some extent, keep mosquitoes from bothering, and a little oil of citronella smeared on the socks while dining will still undoubtedly give comfort to the diner against a few mosquitoes. It is quite another matter when, in a tropical climate, repellents are required to protect soldiers sleeping in a trench or on sentry duty, or to protect troops from malaria. An article such as the present can give little idea of the immense developments in the military use of repellents. Its purpose will be served if it gives the ordinary reader a general idea of the subject.

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MODERN DEVELOPMENTS IN FLY CONTROL

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A review of modern developments in fly control must of necessity be a review of insecticides and their methods of application. The intensive research which has proceeded throughout the war has been designed to answer the immediate problems confronting the Armed Forces in different parts of the world, because armies have to rely upon insecticides more than civilian populations. The established methods of fly prevention by disposal of refuse, incineration, etc. are still used and have not changed. The new insecti-

cides, however, have altered the general problem of fly control, and their effects are discussed in the last section of this paper.

It is to be regretted that the fundamental principles of insect control, modes of action of insecticides, etc., have been largely ignored in face of the urgency of the practical problems. Some work has been done by the U.S. Department of Agriculture, Bureau of Insects affecting Man and Animals, the London School of Hygiene and Tropical Medicine, and the Pest Infestation Laboratories of the Department of

Scientific and Industrial Research Much work remains to be done, but sufficient has been accomplished to show that the formulation of insecticides is a most important problem, and that the development of proper apparatus for the application of insecticides is essential if effective control is to be obtained

All work has been concentrated on the control of *Musca domestica* and flies infesting houses and camps, which very broadly come under the heading of houseflies The limited evidence available on the susceptibility of other muscids is summarized in Section B

Most of the work has been carried out in Great Britain and the USA under central government direction, and for reasons of security has been withheld from publication It is difficult therefore to refer to the original work, though with the end of hostilities it is expected that much of it will soon be published in the normal manner

A. HOUSE FLIES (*Musca*)

The familiar pre-war term "fly spray" is now usually restricted to the type of spray discharged into the air to destroy flies and mosquitoes present in the room at the time of treatment. The advent of DDT, with its particular property of remaining toxic to insects for long periods after its application to wall-surfaces, has resulted in the development of a new and very effective method of control termed "residual spraying." It is probable that this method will gradually replace the older "fly spray" method, though both have their rightful place in a proper fly-eradication programme.

1. Fly Sprays

The shortage of pyrethrum, especially after the entry of Japan into the war, and the enormous demands for fly spray for the Armed Forces, led to intensive investigations to find either a substitute for pyrethrum or an activator for pyrethrum which would allow of a substantial reduction of the pyrethrin content of sprays

No substitute for pyrethrum has been found, none of the new insecticides having the power of giving a quick "knock-down" which is so characteristic of the pyrethrins A wide range of chemicals was tested by U S workers in search for an activator A number of chemicals showed an activating action, the most successful being ethylene glycol ether of pinene (DHS activator), N-isobutylundecylenamide (IN-930), sesame oil and lubricating oil.

The introduction of new insecticides proved of value, as it was found that the synthetic chemicals such as DDT, lethane, the thiocyanates, and thanite could be included in sprays containing a reduced pyrethrum content. The effect was to obtain a quick knock-down with the pyrethrum, and a slower lethal action with the second insecticide which ensured that any mosquitoes or flies "knocked-down" would not recover The sprays in use early in the war were based on 3 % lethane, or 2.5 % thanite, with or without pyrethrum These sprays are now obsolete, and to-day the standard British spray for general use is

0.07 % pyrethrins
or 0.05 % pyrethrins + 0.3 % DDT
or 0.03 % pyrethrins + 0.5 % DDT

The U S formula is very similar, and both err on the side of safety Parkin & Green (unpublished) showed that 0.05 % DDT (pure *para-para* compound) plus 0.02 % pyrethrins was not entirely satisfactory for killing flies 0.10 % DDT and 0.03 % pyrethrins was effective in chamber-tests, and used at the rate of 1 fluid ounce per 1,000 cubic feet [1 ml. per m.³] in army huts gave a high knock-down, and a complete kill of flies Gersdorff & McGovran (1944) showed that in laboratory tests, using the turntable method, 0.25 % DDT in kerosene gave 100 % kill of flies, while 0.125 % failed to do so In tests with *Musca* sp., the following combinations were found to be effective both for knock-down and kill

0.03 % pyrethrins + 0.10 % DDT
0.05 % pyrethrins + 0.05 % DDT
2.0 % thanite + 0.10 % DDT
2.0 % lethane 384 + 0.10 % DDT

It has been shown by many workers that DDT alone will not give a quick knock-down, it requires from 10-15 minutes to have an effect on flies However, DDT is an essential ingredient in a fly spray containing a very reduced quantity

of pyrethrum with or without an activator DDT is not essential in such a spray for use against mosquitoes only

Numerous field-tests conducted in the British Army have proved the value of the British formula and shown that it was necessary to use 1 fluid ounce of the spray for 3,000 cubic feet to obtain uniform results

Work by Sullivan, Goodhue & Fales (1942) showed a new method of dispersing aerosols This method depends upon mixing the spray with a liquefied gas held under pressure, so that when the pressure is released, the spray is dispersed as a very fine mist The U S authorities use dichlorodifluoromethane (freon 12), a refrigerant, as the dispersing agent; and the British use carbon dioxide Methyl chloride was discarded as a dispersing agent because of the risk of toxicity, although Wells (1944) used such an aerosol for the control of *Lyperosia irritans* on cattle Formulation of the spray presented many problems, as the spray fluid must be concentrated Lindquist, Travis, Madden, Schroeder & Jones (1945) showed that an auxiliary solvent for DDT was essential in order that high concentrations could be used, and that cyclohexanone was the best substance for this purpose Various formulae have been developed, one of the most satisfactory being 0.3 % pyrethrins, 3 % DDT, 5 % cyclohexanone and 5 % lubricating oil or sesame oil in freon The method, which is fully discussed by Goodhue (1944), has great possibilities and was of particular benefit for the Armed Forces Different types of containers were devised called "bombs", also small containers, "sparklet" bulbs, were developed for use by individuals

ii Residual Sprays

Residual films of insecticides have been one of the greatest advances in insect control The first public indication of the new method came from Wiesmann (1943) who showed that DDT on glass would kill *Musca* and *Stomoxys* after only 30 seconds' contact of the fly with the treated glass, and that the DDT deposit remained effective for 3 months He showed also that two sprayings in cowsheds would almost eliminate flies for one season Many other workers have obtained similar results Lindquist, Madden, Wilson & Jones (1944) in laboratory tests showed that flies exposed in unpainted wooden cages treated with 25 mg DDT per square foot [about 0.09 m.²] were killed up to 265 days after application They also found that the time required for flies to be affected depended upon the time of contact with the treated surface, the time of contact increasing with the age of the DDT film, and also that the type of surface treated had an important bearing on the length of the persistent action.

Blair and his colleagues (unpublished) in semi-field-tests in Palestine, using treated glass and treated wire-mesh screens, obtained similar results, and also found that, with equal exposure-time, the time required for flies to be affected increased with the age of the insecticidal film Several workers in the British Army have obtained similar results in practical field-trials, the results from Italy, East Africa and India suggesting that the type of wall-surface treated is important. For example, in East Africa a report stated that DDT remained effective longer on mud-walled metal-roofed houses than on thatched native huts The effect of the different types of wall-surface has yet to be fully determined

Lindquist, Madden, Wilson & Knippling (1945), from laboratory tests with houseflies, suggest that the solvent for the DDT residual spray is important, for example, 5 % DDT plus 5 % cyclohexanone in deobase was slightly better than 5 % DDT in kerosene They report that on painted surfaces a suspension of DDT was better than DDT in solution, and other workers have found that emulsion-sprays are sometimes more effective than solution-sprays All workers are agreed that dusts are much less effective than solution-, suspension-, or emulsion-sprays The effect of temperature has been studied by Lindquist, Wilson, Schroeder & Madden (1945), preliminary results indicating that whilst DDT is effective over a wide range of temperature, a higher final mortality of flies was obtained when the temperature after exposure was low (70° F) as compared with 80-100° F The opposite effect was obtained with pyrethrum

The modern aerosols contain DDT, and it has been suggested by Schroeder, Madden, Wilson & Lindquist (1945) that a residual action can be built up by continued use of DDT aerosols These authors state that such a method of obtaining a residual action is unreliable, and is no substitute for the proper method of using a residual spray

It has been shown that benzene hexachloride (666, gam-mexane) has the same property as DDT of producing a residual action. It has been found by several workers that, weight for weight, it is quicker-acting than DDT, although there is some doubt as to whether the length of residual action is as great (Craufurd-Benson, unpublished). Less work has been done with this promising insecticide because DDT was available to the Army at an earlier date, and the work was consequently concentrated on it.

iii. Insecticidal Paints and Distempers

Campbell & West (1944) were the first to show the value of incorporating DDT in paints. Using an oil-bound water-paint containing 0.5% DDT, they obtained 90% kill of flies after a 48-hour exposure, the weight of DDT per unit area not being stated. Busvine (unpublished) found that residual sprays were more effective than distempers, 0.01 mg per cm² of DDT applied as a kerosene solution giving 100% kill, whereas a distemper to obtain the same effect, had to be applied in a concentration of 0.4 mg per cm². Barnes (unpublished) found that a distemper, made by adding an oil to a solution of casein in alkaline aqueous borax, was more effective against *M. domestica* than against bedbugs. A deposit of 0.4 mg DDT per cm² in a dry distemper film gave 83% kill of flies after a 45-minute exposure. In conclusion, Barnes considered distempers uneconomical compared with residual sprays, and found that

- i DDT in distemper was more effective if incorporated in large particles than as fine powder,
- ii weight for weight, DDT was more effective if added after milling than before,
- iii the temperature of the distemper at the time the DDT was added was of no consequence,
- iv there was no deterioration on storage for some months.

It would seem that the inclusion of DDT or any other persistent insecticide has possibilities as a practical method of controlling insects, though at the present time more work is required on formulation of the paint or distemper to make the DDT more easily accessible to the insect.

iv. Larval Control

Little has been published on the use of insecticides for larval destruction, though a considerable amount of work has been done. McGovran, Richardson & Piquett (1944) showed that DDT, borax, and thiourea, were toxic to 3rd-stage *M. domestica* larvae breeding in an artificial medium. Simmons & Wright (1944) treated manure-heaps with DDT emulsions at the rate of 0.6 US gallon per cubic foot [80 l per m³] of manure, and obtained satisfactory larval control at a concentration of 0.1% DDT. Good results were obtained with *Stomoxys* larvae. Some American workers, principally Lindquist and Wilson, have investigated the use of DDT, paradichlorobenzene (PDB), orthodichlorobenzene (ODB), benzene hexachloride, and a number of other insecticides. DDT has been found relatively ineffective against fly larvae, but breeding areas treated with DDT kill adult flies settling on the treated areas, and also newly-emerging flies. PDB and ODB are both effective against eggs and larvae, and benzene hexachloride has been found effective against larvae and adults. Some workers are not in agreement with the findings on DDT and benzene hexachloride, their reports stating that these insecticides do not kill fly larvae or prevent breeding. From the various reports it seems that fly larvae are very resistant to insecticides, probably because of the difficulties of penetrating the mucous film around the body. The *Bulletin of the U.S. Army Medical Department*, No. 86 (March 1945) recommends the use of DDT residual spray at a rate of 200 mg DDT per square foot. Later work suggests that paradichlorobenzene should be included.

Trials in Italy by Craufurd-Benson (unpublished) showed that DDT and benzene hexachloride had no ovicidal, larvicidal or pupicidal action. Good results were obtained against adult flies. Evidence was found that the treatment of manure-heaps, refuse-pits, etc., to prevent fly-breeding was a valuable method, as the adult flies were killed. It appeared that the larvae avoided the action, if any, of these insecticides by migration into the manure or refuse and away from the treated surface.

The treatment of carcasses, human and animal, has been a big military problem. Variable results have been obtained

in the British and American Armies with DDT, benzene hexachloride, and paradichlorobenzene. The British Army in North Africa and Italy used creosote, as being quick in destroying larvae and in masking the cadaverous odour.

B. OTHER MUSCIDS

A limited amount of work is available to show that a number of species of *Muscidae* are susceptible to DDT residual sprays. Wells (1944) sprayed cattle with DDT solutions and emulsions for the control of *Lyperosia (siphona) irritans*. Using 2-3 pints [about 1.1-1.7 l] of spray per cow, cattle were kept free of flies for 1 week, and partially free for 2 weeks. An emulsion spray of 0.2% DDT was ineffective. With a DDT aerosol, cattle remained free from *Lyperosia* sp. for a week, but all effect was lost by the end of the second week.

Van Leeuwen (1944) obtained a big reduction of flies infesting cowsheds, sheep-pens and pigsties by using DDT residual sprays and, if the doors were closed, all flies trapped inside died in 4 hours, even 3½ months after application of the spray. Blakeslee (1944) controlled *Stomoxys calcitrans* by three applications of a 2% DDT spray at 10- to 12-day intervals in screened stables, using one US gallon per 250 square feet [about 0.14 l per m²]. The same author protected horses by spraying twice daily. One application was completely effective for one hour, it gave partial protection for the next 1-3 hours, and the DDT remained toxic for several days, though failing to give any practical protection against fly-worry. Buxton (1945) reported a big reduction of *Stomoxys* sp. and haematophagous *Musca* sp. in West Africa following the spraying of one cow in a small herd. Various other reports have been made on the good results obtained in cowsheds, dairies, etc., following DDT residual spraying.

Buxton (1945), in collaboration with Nash, has stated that *Glossina* spp. are susceptible to cloth impregnated with DDT, illustrating a new method of control previously used only for louse control.

Little work has been done on larval control beyond that cited in the previous section. Some American reports state that *Cochliomyia macellaria* larvae can be killed with paradichlorobenzene or benzene hexachloride.

DISCUSSION

The introduction of the new insecticides, such as DDT and benzene hexachloride, which have persistent actions against insects, has opened up new ways of dealing with the fly problem. However, it has been found in the Armed Forces that these new methods are not substitutes for the standard methods of fly prevention, and are only ancillary to them. As ancillary methods they are extremely valuable.

The modern fly sprays and aerosols are a big advance on the older sprays containing pyrethrum only, or lethane, thanite, etc., but in use they are limited, as they will kill only those insects present at the time of application. The residual sprays open up prospects of complete fly-eradication, as the one treatment is effective for many weeks, and the toxic action of the insecticide is exerted at all times compared with the short time of action of the normal fly spray.

Practical experience has shown that certain principles must be observed in the use of residual sprays. First, the object of residual spraying is to reduce the insect population (density), and not to kill individual insects. This means that all possible resting and hiding places of the fly should be treated, treatment of individual rooms or houses is of little value. This principle is of particular importance in larval control, where it is often impossible to treat all breeding areas. The second principle is that DDT, benzene hexachloride, etc. are true insecticides, and not insect repellents. Thus the insecticides must be applied to those places where flies normally rest. Treated walls etc. will not prevent flies entering a room. Thirdly, the length of persistent action of DDT is dependent upon three interlinked factors

- a the amount of DDT applied per unit area,
- b the age of the insecticidal film, and
- c the time of contact of the fly with the treated surface.

There must come a time, when, due to weathering and loss of DDT or benzene hexachloride, etc., the number of flies that are killed is too small to effect a reduction in the fly density, and yet individual flies may still be killed.

It has been shown experimentally that residual sprays can

replace ordinary fly sprays, particularly inside buildings which are screened or where the entrance and exit of flies may be restricted

Fly sprays and aerosols are useful in unscreened rooms, private houses, dairies, etc., where an immediate kill of flies is required, also in rooms and buildings where all inside surfaces cannot be treated. Therefore, the combined use of

residual sprays and fly sprays, or aerosols, may sometimes be necessary

There is undoubtedly much work to be done on the use of insecticides against fly larvae and the prevention of fly breeding. All workers are agreed that, at present, the use of insecticides does not replace the normal fly precautions of screening, sealing, incinerating, etc.

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SCRUB-TYPHUS: A DISEASE OF MAN TRANSMITTED BY MITES

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Some three years ago an appeal was made to London from the Assam-Burma theatre of war for help in dealing with unexpected and alarming outbreaks of an acute infectious disease, the features of which were recognized to resemble those of tsutsugamushi disease as recorded in pre-war years in certain eastern countries, principally in Japan, Formosa, Indo-China, Malaya, the Netherlands' East Indies and Queensland. At about the same time, quite independently, the U.S. High Command in the South-West Pacific area appealed to Washington for assistance in dealing with a disease that had the same characteristics as that encountered on the Assam-Burma front. That the fears on which these appeals were founded were not misplaced has been confirmed by the mounting incidence of this disease, although considerations of security restrict, at the time of writing, what may be divulged, it may be stated that one or more men were dying daily of the disease, that the mortality-rate averaged 10-15%, and that in three times that number the period of convalescence has been very protracted. The psychological effect on the troops has been considerable.

The many detailed descriptions already extant of the various features of the disease, from British, French, Dutch and Japanese, render a recapitulation of these unnecessary. It is proposed in this short paper to touch only lightly on known cardinal features, and to bring into greater relief the nexus of events that has caused this disease to soar from obscurity to prominence, and the intensive effort of the medical entomologist and the virus worker to check its effects on the fighting efficiency of the troops at risk.

The Disease in Pre-war Years

Scrub-typhus is none other than tsutsugamushi disease, long known to have its classical home in Japan and Formosa. As with so many diseases that have lurked unsuspected in contiguous countries, its first recognition led to a confusion of tongues as to nomenclature. Many place-names or other descriptive names, based on supposed differences of a minor character, were given to it, but exhaustive laboratory studies, especially cross-protection tests between strains from various territories, quite clearly indicated the identity of these alleged variant forms with the classical tsutsugamushi of Japan and Formosa.

It is an acute infectious fever, of some 15 days' duration, characterized by severe headache, a rash, and a lesion at the site of inoculation that is first macular, then papular, and in many cases progresses to form a small black necrotic ulcer. In the second week, nervous and pulmonary complications are usual, and from the 9th-12th days the patient,

with few exceptions, is critically ill. The mortality-rate has varied from 50% in Japan to 15% in Malaya and 5-10% in the Netherlands' East Indies.

Invalid though the term "scrub-typhus" be, it has merit, for "scrub" marks its epidemiology, and "typhus" its kinship with the group of typhus-like fevers, one or more members of which are found in each of the five continents. Regarding the latter association, not only are its clinical features similar to those of other forms of typhus fever, but its pathology, causal organism and serology also. Thus the pathology is primarily an affection of the smaller arterioles and capillaries, none but the most experienced pathologist could differentiate between tissues submitted from cases of any of the other members of the typhus group, i.e. louse-borne, flea-borne and tick-borne typhus. Its causal organism is a rickettsia, the *Rickettsia tsutsugamushi*, easily visible under the microscope but not cultivable in the absence of living cells. Serologically, convalescent serum will agglutinate one of the *Proteus* X strains, in this case the OXK strain.

In its experimental pathology and its epidemiology, however, it differs widely from the other typhus fevers, consequently the striking advances that the impact of war has brought in the prophylaxis of louse-borne typhus have no application in scrub-typhus. It is a disease of the countryside. Its maintenance in nature is secured by a rickettsia-mite-rodent cycle. The mites as yet incriminated with certainty are the *Trombicula akamushi* in Japan and Formosa, and the *Trombicula deliensis* in Malaya and the Netherlands' East Indies. Only the larval stage of these mites feeds on the rodent, the nymph and adult being, as far as we know, vegetarian; the larva feeds once only, for approximately three days, the virus is congenital in the mite. The rodent host of the mite is a field vole in Japan and the rat in Malaya; it is known, however, that certain migratory birds can carry the larvae, and it is thought that by their agency the disease may have been implanted in distant regions.

Impact of the Disease on the Armed Forces

In pre-war years the disease rarely obtruded in medical statistics. Since it is limited to "islands" of scrub-country in primary and, especially, in secondary jungle, few were then at risk except those whose vocation or recreation took them into such areas. Compared with such diseases as malaria, tuberculosis, pneumonia and dysentery, scrub-typhus was of little importance. With the outbreak of the Japanese war, and the ebb and flow of jungle warfare that followed, a thousand were now exposed where previously one had been.

the rodent was supplanted by man as a host of the infected larval mite in like proportion, and the incidence soared

It was already known that the disease clings to areas of countryside, once infested, so that local outbreaks amongst troops fighting in such areas were not unexpected. But surprising, though quite explicable, has been the very large number of these localized outbreaks, man has, of course, gone into these infested areas, hitherto "silent", in which this rickettsial disease has long existed as an infection of mites and rodents, and has, to his cost, become the indicator of the presence of the infestation and infection of the areas

Counter-measures

The problem of counter-measures was one of many facets. About the causal rickettsia, much was already known on which intensive vaccine investigation could readily be grafted. But in pre-war years, owing to the overriding claims of malaria on the time of the medical entomologist working in the East, the entomology in all its aspects had lagged far behind the virus work. Need to dispel the despondency induced by this "mystery" disease was also evident.

The measures taken can best be discussed under the headings "educational", "anti-rat", "anti-mite" and "anti-rickettsial".

Educational

The soldier is aware of the connection of malaria with the mosquito, he sees the latter, and is not surprised should malaria break out. In the case of scrub-typhus, however, the larval mite is less than half a millimetre long, it feeds for only three days and in so doing causes no irritation, so that during the incubation period of disease (7-21 days) the victim is entirely unaware of having been bitten. His objective impression of the disease is that formed by seeing first one, then another, of his comrades carried down the line, with high fever and perhaps the cyanosed and drunken appearance of the well-established infection, later he hears of the considerable death-rate, and he is left with a depressing impression of a silent enemy against which he is helpless.

In the face of this, an energetic educational campaign designed by lecture, film and poster to strip the disease of its imputed mystery was clearly necessary, and is now in being. An excellent cine-film showing the life-history of the mite, its habitat, the technique of certain counter-measures, and other relevant features, has been made, the anti-malaria organizations are being utilized to disseminate information as to those counter-measures that are known and those that are in immediate prospect.

Anti-rat

Outbreaks of the disease have usually been associated with the presence of an abundant rat-population. Obvious sites for camps or bivouacs are areas of secondary jungle, i.e. areas once cleared of primary jungle by indigenous peasants for the planting of grain or other crops, and abandoned by them when the fertility of the soil declined. Such areas become infested with rats, attracted by a ready food supply, and with the rats come their parasites, the mites. After feeding, the larval mites leave the host, and completion of the life-cycle takes place in the soil in the vicinity. Should either the rats or the larval mites be infected with *R. tsutsugamushi*, the establishment of the area as a "typhus-island" is assured.

Information is still lacking as to whether a larval mite that, owing to the death of its rodent host, drops off it when only partially fed will at once undergo metamorphosis to the nymphal stage, or will first resume its feeding on another host, which in the case of a camp-site might well be man. If it re-feeds, then the killing of rats on such a camp-site is clearly inadvisable unless accompanied by immediate disposal of the rat and its attached mites by burning, the latter is the procedure recommended. If it does not re-feed, then the killing of rats will be of no immediate value in the suppression of an outbreak, not until the cycle larva-nymph-adult-egg-larva has been completed could the larva, by its progeny, contribute to the outbreak of infection. The indications are at present that the life-cycle requires some three months for its completion, but that is only by analogy with what obtains in species of mite other than those found in recent theatres of war.

Anti-mite

Counter-measures of this nature fall broadly into two categories, (i) measures of "mite-avoidance", i.e. directed to avoidance of contact with the mite, and (ii) measures directed to poisoning the mite.

1 *Mite-avoidance*—Many practical methods are in use. One, the use of local labour in the dangerous task of clearing scrub, rests quite securely on the observation in many known sites that indigenous populations are much less susceptible to scrub-typhus than are recent intruders into those areas, it is inferred, and is probably true, that attacks of the disease in early childhood, which are usually mild, have conferred an immunity. Others rest on the fact, and in degree of effect are limited by the fact, that the larval mites prefer conditions to be humid, and will burrow some 5-6 inches [12-15 cm] into the soil should conditions become excessively dry. Thus the "civilizing" of an area by the cutting of paths, and by the strewing of such paths and of tent floors with sand, will lead to a fall in the incidence of the disease. Bulldozing a camp-site will presumably remove mites in proportion to the degree of thoroughness applied, and is a recognized procedure. Spraying from the air with DDT is not recommended, since very little of the fluid would reach the mites, and then only those mites which are on the surface, probably DDT applied by hand-sprayers at ground-level would be more successful in reaching mites lurking beneath leaves and other debris. Burning off the surface scrub by the agency of flame-throwers will probably reduce the risk of infection by killing the mites on the surface of the soil, but will leave unaffected those at deeper levels.

ii *Mite-poisons*—The work of McCulloch and his team of entomologists in Australia on the evaluation of mite-poisons has given to us our most effective single weapon against scrub-typhus. Of many substances investigated, DDT, dimethyl phthalate, and dibutyl phthalate, were the most promising, and work was concentrated on them. Uniforms in use in the South-West Pacific theatre were impregnated with one or other of these substances, were washed in different ways (with cold or hot water, with and without soap, etc), and for a varying number of times, and were exposed to direct sunlight, to rain, to muddy water, and so forth. Under each set of conditions the "stopping-time" of those larval mites suspected to be vectors was observed.

The conclusions of these observers were that (a) none of these three impregnating fluids repelled mites, but that they poisoned them, (b) of the three, DDT was the least effective, inasmuch as it took much longer to kill, and lost its effectiveness after one washing of the clothing, (c) although dimethyl phthalate killed the mites in about half the time (2 minutes) taken by dibutyl phthalate, the latter fluid remained effective after six or seven washings of the clothing, as opposed to three washings with the former fluid.

Dibutyl phthalate has therefore become the impregnating fluid universally used against larval mites in the eastern war, with dimethyl phthalate as a substitute where supplies of the former are temporarily scarce. In the field, the Australian Forces consider that the use of dibutyl phthalate has averted fully 75% of the incidence of scrub-typhus.

Quite recently, the similar use of benzyl benzoate has been advocated on the basis of experiments made by American workers in the Panama Canal Zone, and bids fair to prove equally efficient in the field.

Anti-rickettsial

Against the established rickettsial infection in the human, penicillin and the chemotherapeutic agents, methylene blue and *para*-aminobenzoic acid, have entirely failed, the two latter in spite of very promising results in animal tests. The use of rabbit anti-scrub-typhus serum, likewise promising in animal experiments, will probably fail because of the extreme difficulty in obtaining patients in the very early stages of the disease, when alone it can be expected to have some mitigating effect.

Of vaccine production much could be written, but little may be divulged. The success in louse-borne typhus of the yolk-sac vaccine from the infected hen's egg, introduced by Cox and refined by Craigie, has naturally prompted exploration of the possibility of applying a similar technique to the virus of scrub-typhus. Other and even more promising lines of approach have been followed. The next few months should reveal the degree of success achieved.

THE DESIGN AND USE OF SPRAYERS FOR INSECT CONTROL

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The question of the design of sprayers for use with insecticides has received considerable attention during the war as a result of the demands of the Armed Forces for equipment for use in the control of the insects carrying malaria, dysentery and typhus. Much of the spraying apparatus available had been designed originally for other purposes, such as agricultural spraying, paint-spraying or for light household use. As a result there was wastage of valuable insecticide and the equipment often did not withstand military use. In the design of atomizing nozzles little attention had been given to the effect of particle-size upon toxicity, and it had been generally assumed that any fine floating mist would be suitable for use against mosquitoes and house-flies.

Carefully controlled biological tests have shown that the general appearance of a spray is not a reliable guide to its lethal effect, and, furthermore, that some very fine mists or aerosols have little lethal effect on house-flies.

Many different types of sprayer were available which produced a spray with good physical properties, but which for other reasons, chiefly mechanical, were unsuitable for the specialized military requirements.

TYPES OF NOZZLES AND SPRAYERS

Types of Nozzle Used

There are four main types of nozzle. In the simplest or "opposed jet," the liquid is atomized by passage of air (at right angles) across the top of the dip-tube. This nozzle will give good atomization, but the distance between the jets is rather critical and there is a strong tendency to spit. Spitting is always more pronounced with a sprayer with intermittent action than with one giving a continuous spray.

In the "swirling jet," liquid only is passed through the nozzle. Some form of swirling plate is used behind the nozzle orifice, having two or more fine slots cut obliquely in it, the object being to produce turbulence in the liquid and then to expel it under pressure through an orifice. This type of nozzle usually produces a rather coarse spray, and heavy particles predominate which quickly fall out of the spray-cloud.

The "mixing nozzle" depends on mixing air and liquid before they are expelled, the object being to force a froth through an orifice and then to expand it. The atomization is good and there is little tendency to spit.

The final type of nozzle is a combination of the swirling and mixing nozzles, the liquid being mixed with air forming a froth before reaching the swirling plate. This nozzle gives good atomization and practically no spitting.

Hand Sprayers

Of the different kinds the simplest is the hand sprayer. It consists of a simple piston-type pump, a container for the insecticide, and a nozzle. By means of the hand-pump, air under pressure is delivered to the nozzle, and the insecticide is either conveyed from the container to the nozzle through a dip-tube by suction created in the nozzle, or forced up the dip-tube by air pressure in the container. A valve may be fitted in the end of the pump so that pressure is maintained in the container, in which case spray-production is continuous, if no valve is fitted the spray will be intermittent with each stroke of the pump (see Fig. 1).

Knapsack Sprayers

The knapsack sprayer was developed from the hand sprayer. The container is very much larger, usually holding between 1-3 gallons [about 4.5-13 l], and is carried on the back. Usually, a short length of flexible hose leads from the container to a short lance which carries the nozzle. The sprayer is worked by a pump in the container, which has a handle arranged so that the operator can keep it in continuous action. The nozzle used on knapsack sprayers is nearly always of the swirling type with a consequent coarse spray and usually a heavy delivery. An improved form is the pneumatic sprayer, in which the container is made to with-

stand pressure and is only about two thirds filled with liquid. The remaining space is filled with air at a pressure of about 80 pounds per square inch [about 5.6 kg per cm²]. This air is then used to expel the liquid through the nozzle, thus avoiding the labour of continuous pumping. A cock, or simple release-valve, controls the delivery of the spray. It is possible to use a foot-pump to charge the container instead of the hand-pump usually fitted, a heavy-lorry pattern foot-pump being preferable.

Power-operated Sprayers

The next class of sprayer involves much heavier equipment. The air may be supplied either from a rotary blower, such as a large vacuum-cleaner, or more usually from a compressor. The compressor may be driven by an electric motor or by a petrol engine. The compressor charges an air receiver, which absorbs the pulsations of the compressor and maintains a constant supply of air. The air is usually taken from the receiver through a reduction-valve which can be adjusted to give any required pressure within the range of the compressor. The air is then finally led through a filter-unit which removes oil and moisture. All these units are assembled either on a portable frame or on a chassis fitted with wheels. If the installation is to be on a permanent site, a stationary compressor mounted on a bed-plate can be used.

Air from the compressor is delivered to the spray-guns by means of reinforced rubber hose which is fitted with couplings. The hose is usually $\frac{1}{4}$ -inch [about 6.25 mm] bore and supplied in any length required. It has been found in practice that the best length for convenient handling is about 60 feet [about 18 m]. This hose should be supplied on a hose-reel for transport.

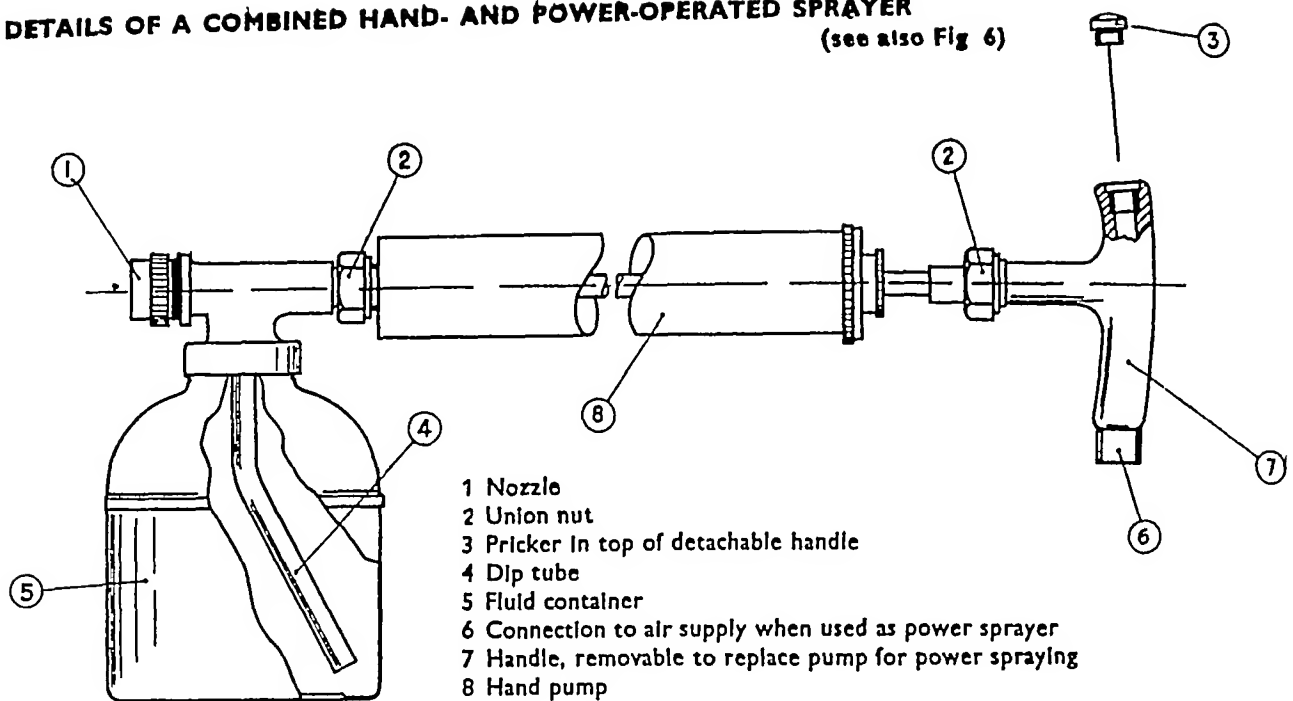
Spray-guns of all kinds are available, among which are guns used for spraying light oils such as paraffin, known as oil- or oil-washing spray-guns, and paint spray-guns. There is manufactured at present a gun which has been designed for use with oil-based pyrethrum insecticide, and is used as part of the equipment for the Armed Forces. In general, the nozzles on all these guns consist of an arrangement of cones, and are unlike the nozzles used on other forms of sprayers. The air is usually led through a central aperture in the male cone, and the liquid into the conical annulus between the male and the female cones (see Fig. 2). The liquid meets a stream of air at high velocity and is in this way broken up and discharged through an orifice in the outer female cone. Very good atomization can be obtained and there is no spitting from this type of gun. The nozzle can be adjusted to give a range of atomization. The gun may be fitted with a container in which the liquid is fed to the nozzle by suction through a dip-tube, or the liquid may be fed to the nozzle by gravity. The largest size of container fitted to the gun is about a quart [about 1.14 l] but larger amounts of liquid, up to 3 or 4 gallons, can be fed to a gun of the paint-spray type by means of a separate pressure-feed container. This necessitates a liquid-supply hose to the gun in addition to the air-hose.

Other Types

Other sprayers which should be mentioned include an aerosol sprayer, which disperses a very fine dry spray by means of baffles round the nozzle so that only the very fine particles are allowed to pass, the larger particles being caught and returned to the well or container of the sprayer. The mist is dispersed from the sprayer by drift, there being virtually no throw.

Self-acting sprayers depending on a compressed gas for their action have also been used for insecticides. In their simplest form these consist of a container, dip-tube and sealing device. The container is partly filled with a suitable insecticide and the remaining space filled with a compressed gas. Freon and carbon dioxide have been used to charge the containers. The sealed end of the dip-tube is arranged so that it can be broken off or opened when required, when the gas in the container propels the liquid out of the dip-tube in the

FIG. 1 DETAILS OF A COMBINED HAND- AND POWER-OPERATED SPRAYER
(see also Fig 6)



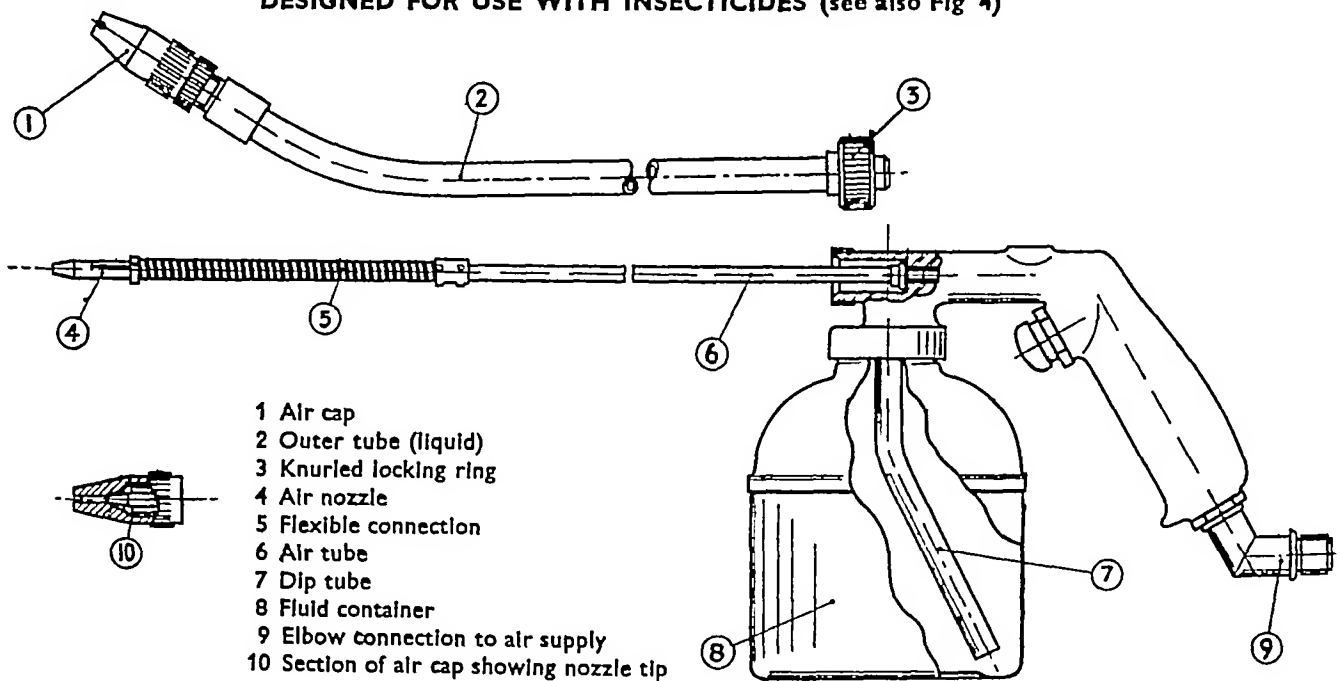
orm of a fine spray These sprayers are small, so that they can be carried in the pocket and used as the occasion arises One of these sprayers takes the form of a small steel bulb familiar before the war in its use for charging soda-water syphons Most of these sprayers cannot be recharged, and their application is limited (Fig 3)

FACTORS IN THE CHOICE AND DESIGN OF A SPRAYER

In choosing a sprayer, two things must first be decided, the insecticide to be used, and the extent and site of the infestation

to cause the particles to adhere to the surface on which they are sprayed and not to bounce off It is also desirable that the cone of spray should cover a wide area, as the surfaces that have to be dealt with are usually large It appears that a nozzle of the swirling-plate type is the best to use for film application, as the nozzles which depend on air for the break-up of the liquid cause the particles to bounce off the surface too much The spray has to be moderately fine to coat the surface evenly and not cause running of the liquid Also, as the surfaces which have to be coated are usually large, the container should be of sufficient size to avoid frequent filling For this reason hand sprayers are not very suitable for applying films

FIG 2 DETAILS OF AN OIL SPRAY-GUN
DESIGNED FOR USE WITH INSECTICIDES (see also Fig 4)



If a water-based insecticide or an emulsion is to be used, the equipment must be rustproof If an oil-based insecticide is used, flexible hose to convey the liquid and all washers must be made of an oil-resistant material (Leather washers are not satisfactory) Endless trouble can otherwise be caused by constant blocking of nozzles

The action of the insecticide is also important For example, pyrethrum sprays give the best results when applied as a mist which will persist in still air for an appreciable time, whereas it appears that the DDT sprays are best applied in the form of a very thin coating or film to suitable surfaces Therefore if a mist spray is required, the atomization wanted will be reasonably fine with a minimum of heavy droplets If a film spray is required, it is desirable that there should be as little mist produced as possible and that the particles of spray leaving the gun have a low velocity, the object being

Hand-operated Equipment

The nature and extent of the infestation governs the length of time that the control is expected to last, and to a large extent the choice between hand- and power-operated equipment For small rooms, huts, tents, etc., a good hand sprayer is very useful where it is not expected that spraying will have to be carried out at frequent intervals over a long period If a large number of hand sprayers is to be ordered, it is necessary to ensure that variation in performance between individual sprayers is minimal The sprayer should be as light as possible without being unduly weak in construction so that it cannot be easily bent or dented, particularly the pump barrel Operation should be smooth and easy (It should be mentioned that hand sprayers have been designed which are physically impossible to use for more than a few minutes at a time)



FIG 3

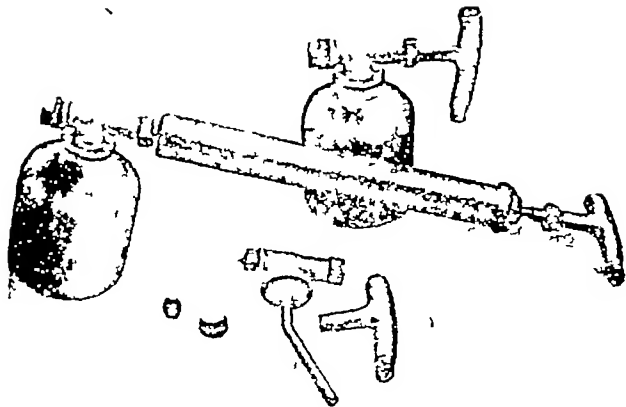


FIG 6

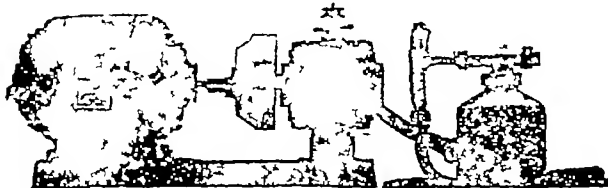


FIG 7

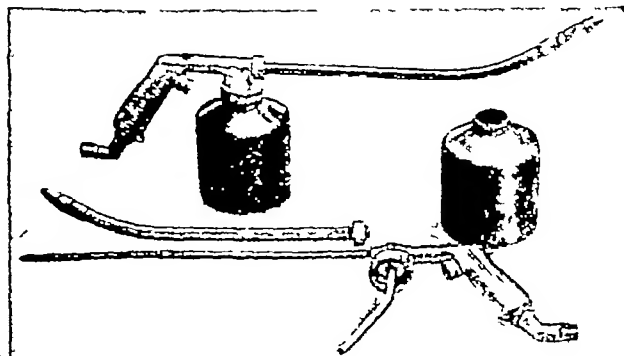


FIG 4

FIG 3 Selfacting sprayers showing how the smaller-bulb type is broken to release the spray

FIG 4 Oil spray gun designed for use with insecticides (see also Fig 2)

FIG 5 Lightweight compressor and full equipment
a Assembled
b Protective casing removed and accessory equipment shown

FIG 6 Combined hand- and power-operated sprayer (see also Fig 1)

FIG 7 Sprayer operated from small electric blower

FIG 8 Sprayer operated from air bottles

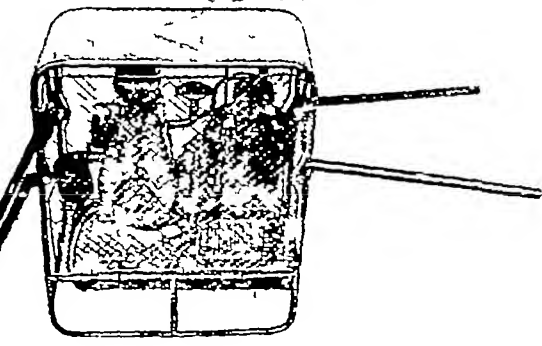


FIG 5a

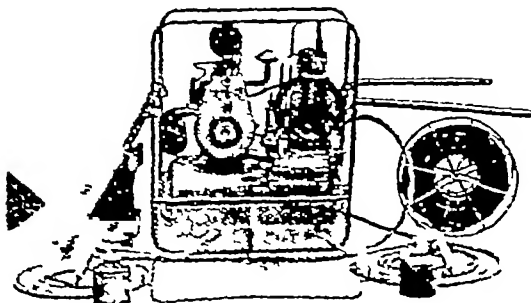


FIG 5b



FIG 8

The sprayer should produce a continuous spray rather than an intermittent one. The design should be as simple as possible, avoiding projections, and nozzles should not be carried on extensions which are easily broken or bent. Protection should be given to the orifice, so that if the nozzle is knocked against anything the orifice is not closed, and this should be as large as possible to overcome frequent blockage. All parts of the sprayer should be readily accessible for cleaning, especially the nozzle, dip-tube, pump-valve, pump-plunger and the inside of the container. A prick of the correct size should be provided as an integral part of the sprayer, as a nozzle orifice can very quickly be ruined by attempting to clear a blockage with pieces of wire (see Fig 1)

Knapsack Sprayers

Where large rooms, barracks and dwellings have to be dealt with, hand spraying will take too much time and larger equipment will be needed. It should be remembered that the easier the actual process of spraying the better will be the results obtained. The operator is able to give more attention to the application of the spray and can continue longer. Therefore in choosing between hand-pumping and power-operation, the latter should always be preferred. The hand-operated knapsack sprayer is not considered desirable, as it is heavy and cumbersome and tiring to operate for any length of time. The pneumatic type of knapsack sprayer, which is charged before use by either a hand- or foot-pump, is preferable, but all these sprayers suffer from the disadvantage that on starting to spray there is a steady fall of pressure in the container and it has often to be pumped up again before it is half empty. The sprayer is heavy to wear, and the operator is easily unbalanced when the sprayer is full. All the knapsack types of sprayer are designed originally for agricultural use, and in consequence the nozzles used give a coarse type of spray and deliver larger quantities of spray in a given time than the other types.

Power Sprayers

In choosing a power-operated sprayer, it is important to consider the output of free air from the compressor in relation to the type and number of guns it is intended to use. The amount of air passing through the gun at any given pressure is expressed in cubic feet [or metric equivalent] per minute. The total air requirement for the number of guns in operation should be 10% less than the output of the compressor, in order to avoid overloading the compressing plant. The compressor should be fitted with an air-relay-valve which enables it to run light when the correct pressure has been reached in the air receiver. When the pressure has fallen 5-6 pounds per square inch [about 0.35-0.5 kg per cm²], the valve comes into operation and starts the compressor pumping again. Thus the compressor should run with alternating periods of idling and pumping. If the total air-requirement is more than that stated above, trouble may be experienced with overheating and loss of pressure.

The pressure-range of the compressor depends entirely on the working pressure of the gun and on the required throw. The blower type of compressor gives a relatively large output of air at a low pressure, whereas the reciprocating compressor of the single-stage type will give anything up to 150 pounds per square inch [about 10.5 kg per cm²].

It has been found that the small portable reciprocating compressor is by far the most useful type, and unless the installation is to be fixed at one site, petrol is preferable to electric drive because of the variation of supply from district to district, and the fact that electricity may not always be available. An objection often made to petrol-driven compressors is that they cannot always be taken inside buildings. Up to 300 feet [about 90 m] of $\frac{1}{4}$ -inch bore air-hose can be used without any serious loss of pressure and by placing the compressor at a suitable place outside the building and running the air-hose in through convenient doors or windows, this objection can usually be overcome. If longer air-hoses are required they should be of larger bore, $\frac{1}{2}$ -inch if necessary.

The compressor can be used to work other types of sprayer than the oil or paint spray-gun. Pneumatic knapsack sprayers may be driven from a compressor by replacing the pump or pump-connection with an adapter for an air-hose. If a reducing valve is part of the equipment of the compressor, it can be used to give any steady working pressure required

in the knapsack sprayer, and this pressure can be maintained. If no reducing valve is fitted, one can easily be inserted between the compressor and sprayer.

Unskilled labour is often given as a reason for using simple hand-operated sprayers. It has, however, been found that unskilled labour can easily be taught to handle and work a modern power-operated sprayer, and that the adaptability of the power-operated sprayer outweighs that of the hand-operated type. Speed and ease of operation are important factors in favour of power-operation. As the modern compressor outfit is automatic in its running, and maintenance is simple, the operator is able to give undivided attention to the application of the spray.

RECENT DEVELOPMENTS

Developments in the design of spray-guns for power-spraying have produced a satisfactory atomization using very much smaller air-flows, so that lighter and smaller compressors could be used. Formerly the air consumption required for oil and paint spray-guns was about 2.5-4.5 cubic feet [about 70-130 dm³] per minute, oil spray-guns having the higher consumption. A spray gun of the oil type (Fig 4) has now been designed which uses less than 1 cubic foot per minute. Two guns of this type can be run from the light form of compressor shown in Fig 5, which has an output of about 3 cubic feet per minute and weighs about 140 pounds [about 63.5 kg]. The compressor is equipped with drop-handles of the stretcher type, and was designed for military use in country difficult for transport.

Another type of sprayer has been designed to have a wide application, as it can be used as a simple hand sprayer, or worked from various sources of power. This sprayer (Fig 6) uses about $\frac{1}{4}$ a cubic foot of air per minute and at present is designed to give a spray of the mist type. All the recommended features of design are carefully followed, in that every part is easily accessible for cleaning, the nozzle orifice is protected from damage, and a prick of the correct size is provided in the handle for cleaning. If it is desired to use this sprayer as a power-operated gun instead of a hand sprayer, the pump-barrel is detached from the body of the sprayer and from the hollow handle, and this handle is attached to the body in its place. The lower end of the handle is machined to take an air-hose connection, and the sprayer can now be operated from a compressor adjusted to give a pressure between 15-30 pounds per square inch [1-2.5 kg per cm²]. The sprayer can be operated from the small electric blower of the type shown in Fig 7, or several can be operated at the same time from the compressor illustrated in Fig 5.

In Fig 8 is shown the experimental apparatus for a trial in which the same sprayer was operated from air-bottles carried on the back of the operator. These air-bottles are previously charged from a compressor. The bottles illustrated are charged to 150 pounds per square inch, but smaller bottles and higher pressures could be used to advantage. The air is drawn off through a reduction-valve set to give about 20 pounds per square inch. There is sufficient margin of air in the air-bottles to allow complete discharge of the sprayer-container before the pressure in the air-bottles has fallen to 20 pounds per square inch, so that there is a steady pressure supplied to the sprayer the whole time.

The present development of sprayers for use with insecticides to control insect infestations of medical importance shows that there is still much improvement required in the design of sprayers. The importance of the physical properties of the spray has, until recently, been almost ignored, and the mechanical construction of the majority of commercial sprayers leaves a great deal to be desired.

Experience during the war has shown that it is often better to design apparatus based on careful biological testing and sound engineering design, rather than to attempt to adapt or improve existing proprietary equipment. Durability and constructional design are often sacrificed for cheapness. In consequence, the cost of replacements and the unsatisfactory results obtained soon outweigh the initial higher cost of well-designed apparatus. The characteristics of any good sprayer should be that it produces the best type of spray for the insecticide used, and that it has simplicity of design and ease of operation.

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RISKS TO MAN AND ANIMALS FROM THE USE OF 2,2-BIS (p-CHLORPHENYL), 1,1,1-TRICHLORETHANE (DDT) WITH A NOTE ON THE TOXICOLOGY OF γ-BENZENE HEXACHLORIDE (666, GAMMEXANE)

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Risks to man from contact with new insecticides may be anticipated from a variety of sources. Workers in factories engaged in bulk production are continually exposed to dusts or fluid suspensions of these compounds. During the use of insecticides in the field, or for disinfecting buildings, bunks or vehicles, contact is probable, especially when operatives are not properly instructed in hazards. Contamination of foodstuffs and water is a third possibility. To these risks must be added the accidental ingestion of the compound, especially by children, through carelessness in storage. I know of one such instance where a young child swallowed a kerosene solution of DDT and died soon afterwards with typical symptoms of poisoning. Harm from the use of insecticides may thus come from their contact with the skin, as during manufacture, handling, preparation of solutions and emulsions, accidental spillage, spraying and impregnation of garments, from absorption through the alimentary canal after ingestion of contaminated food or water, and through inhalation which brings them into close relation with the immense absorptive surfaces of the respiratory system. To this list may be added several less probable risks, such as eye damage, wound contamination (a possibility which has to be seriously considered during wars), and the handling of pets sprayed against vermin. All of these chances may be met with in man and some of them in animals if DDT and gammexane are widely adopted.

Preparations of DDT

DDT is very slightly soluble in water, so that it has to be used as a dust, in oily solution or as a mist. In the former case it is mixed with clays, talcs, sulphur, etc., and ground into fine powders containing minute particles of DDT in various strengths. If a wetting agent be added to such powders, they can be mixed with water and used as sprays. Oily solutions employ various petroleum oils, especially kerosene, xylene and other solvents for dissolving DDT. In this way, spray-solutions or emulsions are prepared. Aerosols and mists make use of sesame oil, cyclohexanone, freon or other oily solvents as dispersing media. Various agents, such as dimethyl and dibutyl phthalate, pyrethrins which exert destructive actions on insects, may be incorporated with benefit in DDT emulsions and solutions. Absorption into the body, the first stage in production of harmful action, is thus dependent on the physical state of DDT during contact with the surface and body-cavity tissues. In general, it may be said that powdered forms present little risk of absorption, but oily solutions and emulsions can penetrate some of them with ease.

Acute Toxicity Tests

The complete investigation of the toxicity of DDT is possible only through animal experiments, although much information has been obtained from observation and cautious experiments on man. Results from animal work may be applied with some accuracy to humans, although the characteristic difficulty of the toxicologist—the assessment of individual susceptibility—is a source of uncertainty in arriving at the fatal dosage for man. Table I summarizes the lethal figures arrived at by workers in the USA and Britain. DDT has been administered through a number of routes, in various solvents, to an imposing array of animals, with a striking uniformity in results. These figures for acute experiments, i.e. single doses advanced to a fatal level, are given as LD₅₀, the smallest amounts which will kill at least 50% of a group of animals. It may be concluded that DDT applied to the skin, injected subcutaneously—in other words, introduced directly into the body—or administered by stomach-tube is tolerated in large amounts by a variety of animals. From these experiments it is assumed that the

fatal dose for man lies somewhere within this range of lethality, although the possibility that certain factors arising from man's special constitution may make him unduly susceptible cannot be neglected. Such a possibility has to be considered, especially when an action on the central nervous system is a dominant feature. We shall see that this is the case with DDT.

TABLE I
LD₅₀ VALUES FOR SINGLE DOSES OF DDT

Recorded by	Route of administration	Animal	Solvent	LD ₅₀ (mg./kg.)
Woodard, Nelson & Calvery (1944)	Oral	Mouse	Corn oil	448
		Rat	" "	180
		Guinea-pig	" "	>562
		Rabbit	" "	>400
		Chicken	" "	>300
Smith & Stohlmann (1944)	Stomach	Rat	Olive oil	150
		Rabbit	" "	300
		Cat	" "	300
Cameron & Burgess (1945)	Stomach	Rat	Liquid paraffin	800
		Guinea-pig	" "	400
		Rabbit	" "	300
Draize, Nelson & Calvery (1944)	Skin	Rabbit	Corn oil	>940
		Rabbit	Dimethyl phthalate	>2820
		Rabbit	Dibutyl phthalate	>2350
Cameron & Burgess (1945)	Skin	Rat	(Ether kerosene dimethyl and dibutyl phthalate)	3000
		Guinea-pig	" "	1000
		Rabbit	" "	300
Woodard, Nelson & Calvery (1944)	Intra-muscular intra-pentoneal sub-cutaneous	As for oral experiments	Corn oil	Doses higher than those for oral, but action irregular
Cameron & Burgess (1945)	Sub-cutaneous	Rat	Liquid paraffin	1500
		Guinea pig Rabbit	" "	900 250

Chronic Toxicity Tests

It is not easy to summarize with ease experiments on repeated administration of DDT to animals, it is sufficient to say that much smaller doses of oily solutions, when given frequently over an extended period of time, can bring about harmful changes. There is some evidence that cumulative effects may occur, although these are by no means striking. We shall be in a better position to assess this hazard when we possess a complete picture of the extent to which DDT can be absorbed from the body surfaces, the degree of elimination by the excretory mechanisms, and the success of detoxication within the body.

One important conclusion can be drawn from this work. Even if it should turn out that man has a very high resistance to oily solutions of DDT, the lethal figure is not likely to be unduly high and with carelessness in the use of concentrated solutions (10%–25%) the danger zone might well be entered. Men handling such concentrations should take precautions against skin-contact and inhalation of oily solutions whilst food must be protected from contamination. On the other hand, toxic levels are not easily reached when dilute solutions

suitable for insecticidal purposes are employed. Danger to health, it should be emphasized, is likely to arise only from careless use of concentrates. All observers agree that dry powders of DDT present no danger of absorption from the skin, whilst large doses of the pure compound, which would imply huge amounts of the commercial dusts, are required to give injurious effects after ingestion.

Inhalation of finely-dispersed DDT particles in the form of mists and aerosols can lead to harmful effects and death, but it seems that fairly high concentrations are necessary and time of exposure must be long before the danger level is reached. Neal *et al* (1944) conclude that the use of DDT, in 1%–5% solution in 10% cyclohexanone with 85% or 90% freon as aerosols, should offer no serious health-hazards when used under conditions required for insecticidal purposes. Our experiments (Cameron & Burgess, 1945) with heavy mists support this contention.

Human Response to Exposure

There is now available an increasing body of information about man's response to exposure to DDT, though of course due care has been taken in experiments to prevent serious effects from developing. Workers in factories where DDT is being made are carefully scrutinized from time to time, and a watch is kept on operatives engaged all over the world in spraying, etc. With a few doubtful exceptions, nothing has occurred so far which might give rise to alarm. Wigglesworth (1945) has recorded symptoms in a laboratory worker whose hands had been in prolonged contact with an acetone solution containing about 25 g DDT. We have carried out a number of experiments with volunteers wearing undergarments impregnated with 1% DDT (dry-weight basis), and have studied a small group of technicians engaged in laboratory work and bulk impregnation which brought them into contact with DDT. In none of these 58 men were there symptoms suggestive of toxic absorption. A few had slight, transient attacks of dermatitis which may or may not have been caused by DDT. These experiments were planned with the specific purpose of finding out whether soldiers under battle conditions could safely wear garments impregnated with DDT as a safeguard against body-lice. The results left no doubt as to the safety of the method. American observations on men engaged in spraying DDT are equally satisfactory. There must be available, by now, a great amount of clinical experience on this subject, since the use of DDT has become very extensive, it is reassuring that so few incidents have been reported.

Finally, the question was proposed during late 1943 whether DDT-contamination might influence the healing of wounds, a possibility which had to be considered in soldiers wearing impregnated garments. Experimental studies of wound healing in rabbits heavily contaminated with DDT brought reassurance and we found no significant difference between the mean daily rate of closure of standard wounds in untreated and DDT-treated rabbits (Cameron & Burgess, 1945).

Pathology of DDT Intoxication

The symptomatology and pathology of DDT poisoning in animals have been studied in detail. Nervous symptoms and severe damage to the liver are outstanding features. With large single doses of DDT administered by any route, signs of intoxication appear in 12 to 24 hours. The animal feels cold, its fur is ruffled, and diarrhoea may be present. It appears to be nervous and very sensitive to stimuli. Muscular weakness sets in, especially in the muscles of the back, fine and coarse tremors develop in the back and limbs and the animal may shake violently for hours on end. Movement is restricted, staggering, and often spastic. Anorexia and loss of body-weight progress rapidly. Death from respiratory failure occurs in 24 to 48 hours, though it may be delayed for several days. Convulsions are rare, except near the end. In animals that recover, nervous and muscular signs may appear and last for some days, but these eventually disappear and leave no apparent after-effects. Such features may therefore be regarded as premonitory signs of intoxication. They constitute a valuable warning of the approach of danger, for if exposure to DDT is eliminated at this stage, complete recovery follows.

Pathological examinations of acute cases reveals little change in the organs beyond terminal pulmonary oedema, occasionally mild or moderate damage of the liver and

kidneys, fatty degeneration of myocardium, and sometimes haemorrhages in the adrenals. No specific disturbance has been noted in the central nervous system. The axons of the spinal cord and the higher levels of the brain and brain-stem are normal. Sometimes degeneration and destruction of a few anterior-horn cells in the thoracic and lumbar regions of the spinal cord may be discovered.

With repeated exposure to DDT, loss of body-weight, anorexia and diarrhoea are the chief features. Small doses rarely lead to nervous symptoms, but with moderate doses tremors and weakness may come and go. Hypersensitivity to sounds and other stimuli is striking. Some animals seem to recover from these effects only to die at a later stage, others continue to shake until death. The end comes in a quiet fashion and is probably the result of exhaustion. The pathological picture is dominated by liver damage, which takes the form of numerous areas of focal necrosis or large areas of centrilobular necrosis uniformly distributed throughout the organ. Bile-ducts are not injured. The degree of liver damage is sufficient to account for death.

In animals which recover, the dead liver tissue is completely removed by autolysis and solution and phagocytic activity. Repair is complete, and fibrosis does not develop even when exposure to DDT is prolonged. Other features, admittedly inconstant and of minor importance, include degenerative changes and calcification in the renal tubules, fatty degeneration and focal necrosis in the cardiac and voluntary muscles and, in a few animals, degenerative change in certain parathyroid cells. Repeated application to the skin of DDT in various solvents may lead to dermatitis, and there is some reason to believe that certain animals may become hypersensitive. Up to the present there have been no reports of hypersensitivity in man. A mild secondary anaemia, toxic in type, and pronounced leucocytosis are quite common in animals. Leucocytosis seems to be correlated with clinical features of intoxication, and serves as an intimation that the toxic level is being reached. No characteristic change has been seen in the bone marrow, however.

The experimental investigations of DDT poisoning have thus proved of great value, for they show a constant clinical picture in all animals studied and they suggest that certain premonitory features—nervous and muscular, weakness, leucocytosis—give ample warning of the approach of danger.

Risks to the eyes from splashing with DDT do not appear to be great. We have inserted DDT powder into the conjunctival sac without ill-effects.

Conclusion

In conclusion, it may be said that although DDT can induce toxic features and death if abused, there is a wide margin of safety in its use as an insecticide. With low concentrations (0.5%–1%) there is no reason to anticipate any danger to man, even with long-continued exposure. Higher concentrations demand care in handling oily solutions and emulsions, and cleanliness and avoidance of gross carelessness are essential to safety. Contaminated skin-areas should be washed at once with soap and water. The use of gloves and protective garments is advisable. In spraying with concentrates, respirators should be worn. Although there is no danger of absorbing dry powders of DDT from the skin, inhalation of dusts should be avoided. Care must be taken not to contaminate foodstuffs during spraying with concentrates. With dilute sprays it does not seem likely that amounts of DDT sufficient to harm will be retained in the food.

So far no effective antidote appears to have been discovered against severe poisoning, though sedatives are beneficial.

Note on the Toxicology of Gammexane (666)

Unpublished work by Mr F Burgess and myself suggests that this compound is of relatively low toxicity when applied to the skin or administered orally in single doses. Fairly large doses given repeatedly are tolerated. Table II summarizes the LD₅₀ for single doses. If these figures are compared with those we obtained for DDT in the same stocks of animals, it will be seen that, with the single exception of skin-application to rabbits, gammexane is more toxic than DDT. This is especially noticeable in the case of subcutaneous injection, so that we conclude that toxic effects are more likely to follow with gammexane than with DDT if absorption

TABLE II

LD₅₀ VALUES FOR SINGLE DOSES OF GAMMEXANE (PURE γ ISOMER)
(Cameron & Burgess, unpublished)

Route of administration	Animal	Solvent	LD ₅₀ (mg/kg)
Oral	Rat	Liquid paraffin	200
"	Guinea-pig	"	100
"	Rabbit	"	200
Skin	Mouse	Acetone	300
"	Rat	"	500
"	Guinea-pig	"	400
"	Rabbit	"	300
Subcutaneous	Rat	Liquid paraffin	50
"	Guinea-pig	"	100
"	Rabbit	"	75

occurs. But skin and oral tests show that considerable amounts of gammexane can be safely applied to the skin or ingested, and gross carelessness would appear to be the chief source of danger with this insecticide. DDT possesses one advantage, over gammexane in that premonitory signs of intoxication due to its absorption are well-defined and occur with doses well below the fatal level. We have seen no such safeguarding signs with gammexane, when symptoms appear, the end is usually in sight and little can be done to save the animal.

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Symptoms of acute poisoning with gammexane develop fairly rapidly and include the following, in this order

- i Increased respiratory rate, sometimes very considerable
- ii Restlessness, accompanied by frequency of micturition.
- iii Intermittent muscular spasms of the whole body
- iv Salivation, grinding of the teeth, bleeding from the mouth and tongue resulting
- v Backward movement, with loss of balance and somersaulting
- vi Head-retraction, convulsions, gasping and biting.
- vii Collapse and death

In hyperacute cases, this train of events lasts 40–120 minutes, more resistant animals survive 12–20 hours. Rarely death is delayed for several days or even a week, the animal is then very wasted.

Pathological findings are not characteristic. In fatal cases there is marked distension of the stomach and intestines with gas and fluid, dark fluid blood, congested and oedematous lungs, a distended black or bluish liver with patches of necrosis, congested kidneys, contracted dark spleen, and a pale soft brain, sometimes mottled with pin-point haemorrhages. Microscopical examination adds little to this picture. Liver necrosis is neither severe nor constant.

We have not heard of any human cases of intoxication¹ nor do we know of investigations on human subjects. It is to be hoped that a close watch will be kept on the health of all workers employed in the manufacture of this valuable compound and that relevant information will be published.

¹ [Since this paper was received a report has been published (*Brit med J*, 1945, 2, 845) of a fatal case of DDT intoxication, occurring in a child of 19 months who drank about 30 cm.³ of 5% DDT in kerosene.—Ed.]

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REVIEW OF SELECTED PAPERS

Penetration of Insect Cuticle by Water and Insecticides¹

784

SOME NOTES ON THE INTEGUMENT OF INSECTS IN RELATION TO THE ENTRY OF CONTACT INSECTICIDES by V. B. Wigglesworth, *Bulletin of Entomological Research*, 33, 205–218, October 1942

When insects are immersed in refined mineral oils, the cuticle is changed so that the water passes out and appears as droplets in the oil. This effect is most marked where the cuticle is thinnest, it can be accentuated by placing insects in mixtures of oil and alcohol which break in the presence of water. It is also much more vigorous with newly-moulted insects than with those of about a month old. The rate of separation of water from the cuticle is inversely proportional to the boiling point of the paraffin employed. Water is obtained immediately if the insect is immersed in oil after extraction for a long period in cold petroleum-ether. The passage of water is, therefore, due to solution of the lipid content of the cuticle in the oil.

Experiments in which standard amounts of the insecticide, pyrethrin, was applied in various solvents to a uniform area of a test insect, show that the rate of entry decreases as a series of petroleum oils is ascended. The rate of action of the insecticide is much slower in vegetable oils. Petroleum-ether extraction greatly

accelerates the action of pyrethrin in a heavy oil. The entry of the insecticide in a particular solvent is, therefore, comparable to the "water-producing" effect of that solvent. Variation in insecticidal susceptibility between comparable individual insects is proportional to the gross thickness of the inner layer of the cuticle. It appears that this may indicate the importance of the fine canals in the cuticle in transmitting the insecticide. Histological examination of cuticles shows that the oil is adsorbed over the whole area of new or stretched cuticle, but that, in older insects, adsorption is confined to specific cuticle structures, such as the dermal glands. The adsorption of oil is increased by the addition of 5% oleic acid, or of fatty acids or wetting-agents to the paraffin, and these substances accelerate the action of pyrethrin when added to its solvent oil.

785

I. ACTION OF INERT DUSTS ON INSECTS

by V. B. Wigglesworth, *Nature*, 153, 493–494, 22/4/44

II. TRANSPIRATION THROUGH THE CUTICLE OF INSECTS

by V. B. Wigglesworth, *Journal of Experimental Biology*, 21, 97–114, August 1945

Measurements of the desiccation of insects over a wide range of temperature show that transpiration increases slowly during an initial rise in temperature. At a critical temperature diagnostic of each stage of each species investigated, the permeability changes abruptly, and further increase in temperature causes large increases in transpiration. It is known that the outermost layer of the

¹ [Reference should also be made to a detailed discussion of a theory of the relation of structure and permeability of insect cuticle by Dr. H. Hurst *BAIB* 227.]

cuticle is responsible for its waterproofing, so these must be changes in the outer layer

Inert dusts, which have been used to control pests of stored products, are known to act by increasing the permeability of the cuticle. It has been suggested that they acted by adsorbing the waterproofing lipid from the cuticle, but insects rendered immobile and covered with dust, or killed and buried in such material, are not made water-permeable, whereas insects rubbed with dust are readily dried by desiccation. Similarly, insects which drag part of their abdomen over the substrate are equally desiccated when that is covered with the fine dust or when it consists of fine emery paper. If the abdomen is supported they are unharmed. Dusts are effective after being rubbed on the cuticle and either left on it or washed off.

A technique for staining the inner part of the outer cuticle layer shows that stain applied to the outer cuticle surface penetrates only when desiccation has occurred and the fine abrasions due to the dust are revealed. Insects left in saturated air will slowly recover their impermeability, but leave a visible waxy patch over the abraded area.

The application of contact insecticides to abraded areas causes rapid death among insects which are not killed by 3 weeks' application of insecticides to the normal cuticle. Insects inhabiting the soil have high rates of water-loss due to natural abrasion by soil particles, though this is compensated in nature by the high humidity in which they live. This defect may account for the way in which they may be killed by treating soil with appropriate insecticides. These insects have "normal" cuticles if they moult away from their abrasive environment.

Boiling wax-solvents cause great increases in the permeability of insects when they are applied to the cuticle. This is accompanied by total staining of the underlining cuticle surface. The vapour of such solvents increases the permeability of insects very slightly.

A large number of detergents and emulsifiers increase the water-permeability of the cuticle. Staining shows that this is due to the removal of the outer cuticular layer, and the addition of small quantities of an efficient detergent increases the rate of action of contact insecticides enormously, even though the insecticide may be dissolved in an oily base.

It is therefore concluded that a thin film of wax over the whole cuticle surface is responsible for the impermeability to water of most insects, and that this is a most important factor in the insect's resistance to the entry of insecticides. The cockroach forms an exception, for its cuticle is covered with a mobile grease which is mostly removed by dust-adsorption and is unaffected by abrasion.

786

THE CUTICULAR LIPOIDS OF INSECTS

by J W L Beament, *Journal of Experimental Biology*, 21, 115-131, August 1945

The cast skins of insects usually consist of only the outermost layer of the cuticle. These cast skins have a water-permeability similar to the intact insect when they are used as a membrane, but after extraction in lipid solvents they are completely permeable to water. Extraction of quantities of skins gives wax mixtures chemically similar to beeswax. The amount of wax per cuticle is very constant for a particular species, and corresponds to a layer averaging 0.25 micron in thickness over the insect's surface. It bears no relationship to the thickness of the cuticle or of the cast skin.

The melting points of the waxes do not correspond respectively to the critical temperatures in the transpiration of intact insects. The effect on water-permeability of spreading extracted waxes on various membranes shows that their waterproofing powers depend on the surface of the membrane. The waterproofing of comparable wax layers is proportional to the degree of chemical similarity in the membrane to insect cuticle. When these waxes are spread on extracted butterfly wings, waterproofing properties almost identical with those of the species of origin may be conferred, and identical critical temperatures obtained.

The critical temperature is a function of the wax. Layers of wax only a few molecules thick are responsible for most of the water-permeability of a wax layer on insect cuticle. Investigation of the spreading of waxes on water and of their surface, optical and crystal properties at various temperatures, shows that the innermost layer of wax molecules in the insect's protective wax layer is highly organized in co-ordination with the surface of the cuticle. At the critical temperature this organization breaks down, it is also disturbed by lipid solvents, but the force of attachment between wax molecules and the substrate is so great that dusts cannot adsorb the wax from membranes or from the insect. They may adsorb wax from membranes unlike cuticle with no chemical link between the wax and the substrate and, in the cockroach, dusts will adsorb all but the innermost layer of grease molecules.

An analysis of the action of detergents and emulsifiers on waxes spread on membranes shows that they overcome the attraction between wax and membrane, whereas heavy mineral oils which are the normal bases for insecticides may not do so.

Mites

787

THE OCCURRENCE OF MITES (ACARINA) IN HUMAN SPUTUM AND THEIR POSSIBLE SIGNIFICANCE

by H F Carter, G Wedd & V St E D'Abbrera, *Indian Medical Gazette*, 79, 163-168, April 1944

The authors report that mites have been found in the sputum of 17 out of 28 persons suffering from respiratory disorders in Ceylon. Two categories of samples were examined: those taken in the ordinary way, and others taken with special precautions to avoid accidental contamination by mites from the surroundings, since some of the mites found in the sputum occurred in the dust and air of the wards. They proved to be essentially similar.

At least 10 species were found, some of which have not been identified. Those identified were not parasitic species but are commonly found in stored products, debris and dust. Among those identified were species of *Tarsonemus*, *Tyroglyphus*, *Carpoglyphus*, *Glyciphagus*, and *Cheyletus*, the latter two only occasionally.

Before arsenical treatment, one or two mites were found in about 50% of sputum samples taken from mite-infested persons. After treatment the numbers had decreased and many of those found appeared to be in a macerated condition. No mites were found in saliva or nasal washings, which suggested that the mites were from the lungs and/or bronchi.

Three of the mite-infested persons showed an eosinophilia of from 38-66%, and in all these cases the chest condition was improved and the eosinophilia was reduced after arsenical (stovarsol) treatment.

In one case, mites (*Tyroglyphus* and *Carpoglyphus*) were numerous and, since they were present in all stages including eggs and egg-bearing females, the authors consider that the infestation was of long duration and that the mites had adapted themselves to the conditions within the lungs and were breeding there.

As a result of the evidence obtained, the authors suggest that the condition variously known as "pseudo-tuberculosis," "eosinophil lung," "tropical eosinophilia," etc., may, in part at least, be explained on the basis of mite-infestation of the respiratory system.

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PULMONARY ACARIASIS A POSSIBLE CAUSE OF ASTHMA

by E. Soysa & M D S Jayawardena, *British Medical Journal*, 1, 1-6, 6/1/45

In certain cases asthma may be due to the presence of mites in the respiratory system. Such cases tend to occur in operatives working in dusty trades and may often be cured by organic arsenicals.

The patients concerned in this investigation were Singhalese soldiers who were admitted to hospital with asthma associated with eosinophilia of over 4,000 per mm³. Each patient was carefully questioned, but a previous history, or family history, of asthma or other allergic manifestation, was seldom obtained. The existence of alimentary parasitism, which is known to be a common cause of tropical eosinophilia, was excluded. The cases described received only temporary benefit from the usual asthma therapy.

An examination for mites was carried out on sputum-samples which had been collected after rigid precautions had been taken to exclude mites from extraneous sources. The method employed was that already described by Carter, Wedd & D'Abbrera (1944). These observers have described the recovery of mites of the following genera from the sputum of patients suffering from respiratory complaints: *Tyroglyphus*, *Tarsonemus*, *Carpoglyphus*, *Glyciphagus* and *Cheyletus*. The species concerned are those which typically occur in stored products, dust and debris. The process of recovery involves a considerable expenditure of time, and only one sample was taken from each patient.

Treatment was carried out in two stages, first for a period of 10-50 days with routine anti-asthmatic remedies (excluding arsenicals), and thereafter for 6-33 days with arsenical preparations, either stovarsol (27% arsenic) or carbarsone (28.85% arsenic). One 0.26 g tablet of the former or one 0.25 g tablet of the latter was administered twice daily.

The patients were between 18 and 42 years old and had served in the Army from three months to five years. The most significant aetiological information related to occupation and environment. Of the 30 cases concerned, no fewer than 25 were employed in ration stores, or had been concerned with handling rations, etc. The others had also been concerned with dusty trades.

Details of clinical, pathological, radiological and therapeutic observations given may be summarized as follows. The duration of the asthmatic condition varied from two weeks to three years. At the time of admission the clinical picture was that of asthmatic bronchitis. Haematological examination showed total leucocyte counts from 10,200 to 37,000 per mm³, while the eosinophil concentration ranged from 33% to 81%. Mites were found in 11 out of the 21 cases which were examined. Only a few were discovered—rarely more than one or two in each case—partly, no

doubt, due to the fact that observations were usually discontinued after the first mite had been found. Radiological examination showed a fairly typical appearance of diffuse linear striations and mottling which cleared up in a remarkable manner after arsenical treatment.

Routine treatment provided no more than temporary relief, but the response to the arsenicals was uniformly good and sometimes dramatic. In one case asthmatic symptoms of three years' standing were cured in 9 days, and the eosinophil count improved correspondingly. Usually the haematological response was gradual, but the alleviation of clinical symptoms was comparatively rapid. In certain cases the symptoms increased after the first few days of treatment. Carbarsone and stovarsol produced similar improvements in clinical symptoms, but the former usually produced the more rapid haematological response. Nine months after the first patient had been discharged, no recurrence of asthmatic symptoms had been reported, while several patients who were re-examined later showed a normal haematological picture.

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789

PULMONARY ACARIASIS IN MONKEYS

by L. J. Davis, *British Medical Journal*, 1, 482, 7/4/45

In view of the attention recently directed to the possible significance of mites in the causation of pulmonary disorders such as asthma and bronchitis (Carter, Wedd & D Abrera, 1944, ; Soysa & Jayawardena, 1945), the author draws attention to the discovery of mites in a *Macacus* monkey. Reference is also made to a previous case in which acandrs were found in the lungs of a *Macacus rhesus* monkey (Weidman, 1915).

In the present case, small capsules with walls of cellular granulation-tissue were found scattered through the lungs. Dissection showed that the capsules contained mites which were identified as probably *Pneumonyssus* spp. The surrounding lung-tissue was, on the whole, healthy in appearance, although somewhat congested. No haematological studies were made on the peripheral blood, so it is not known whether eosinophilia was present. It is suggested that the mites may normally occur as ectoparasites, but that upon occasion, owing to the habits of the hosts, they may be drawn into the lungs.

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¹ [BMB 787] ² [BMB 788]

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DERMATITIS DUE TO TYROGLYPHUS LONGIOR, GERV,
VAR. CASTELLANII, HIRST, IN CHEESE DUST

By E. W P Thomas, *British Journal of Dermatology and Syphilis*,
54, 313-319, December 1942

The case is reported of a dockside worker, aged 49, who developed dermatitis while handling imported cheeses. When manipulating the crates, each of which contained 2 large cheeses, he became showered with a fine brown dust from the surfaces of the cheeses. About 24 hours after beginning this work he noticed pricking and irritation mainly of the face. On examination he presented a diffuse erythematous dermatitis of forehead, face, ears, front and sides of neck, and flexor aspects of forearms, where there were also a few urticarial lesions. There was slight oedema of the eyelids. He gave no history of previous skin disease although he had done the same kind of dusty work for more than 20 years and had handled all types of dried foodstuffs. His dermatitis soon subsided with applications of calamine liniment.

Four other men were employed with him unloading the cheeses and apparently were all affected in varying degrees. One of these others was also seen at hospital with a milder dermatitis of similar type and distribution.

A sample of the dust was found to contain many mites which were identified by the British Museum (Natural History) as *Tyroglyphus longior* Gervais, var *castellani*, Hirst, the acarus which causes copra itch.

A morphological description of the mite is given together with a list of other members of the Tyroglyphid family which have been reported as responsible for various dermatoses. A great variety of dried foodstuffs and other materials attacked by Tyroglyphidae are also enumerated.

The writer comments on the paucity of references in dermatological literature to eruptions due to food-mites, which suggests that the majority of these acari are harmless to the skin. He could find only one previous record of dermatitis in a handler of mite-infested cheeses. He remarks that the Castellani-Hirst variety of *T. longior* is not generally mentioned among the common mite invaders of cheese. Old cheeses are the ones usually attacked, in Britain the Stilton and Cheddar varieties are those most likely to be infested. The mites eat into the cheese itself and establish colonies. Infested cheeses can be recognized by the numerous cracks and crevices made by the mites and by the fine powdery dust on the surface, which is composed of layers of dead bodies of mites, their faeces and moulted skins, minute particles of uneaten cheese, and the living mites themselves. The most frequent mode of accidental infestation seems to be by flies, and prophylaxis consists in keeping cheese in cool, light, well screened, scrupulously clean places. Paraffining cheeses, if they are kept unbroken, may prevent their being attacked. Infested cheeses should be discarded at once.

The writer emphasizes that the skin reaction in his cases did not suggest a parasitic cause but was a diffuse contact type dermatitis, while the fact that all the men exposed to the infested cheese-dust were affected suggests that the mites or something in their debris acted as a common irritant rather than a sensitizer. The paper contains a bibliography relating to Tyroglyphidae and, from the clinical aspect, there are a number of references to previous case records of mite-eruptions.

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MITES INFESTING CARCINOMA OF THE JAW

by R. E. H Simpson, *Lancet*, 1, 740, 3/6/44

A farmer's wife aged 54 was found to have a growth about an inch long on the lower gum. She was edentulous and the surface of the growth was in part covered with leucoplakia, in part papillomatous. There was earache and anaesthesia in front of the growth. The diagnosis was papillomatous carcinoma invading the mandible. Clinically no glands were invaded. The growth was found to be infested by a mite of the genus *Tyroglyphus*, possibly *T. longior*. The discovery of living mites and eggs and large quantities of mite-faeces in the deeper layers of the growth suggested a long-established infestation. Typically the mites concerned live on cheese, flour and dried fruits.

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SIGNIFICANCE OF MITES AND THEIR EGGS IN HUMAN FAECES

by P Manson Bahr & W J Muggleton, *Lancet*, 1, 81-82, 20/1/45

Mites occur on foodstuffs of all kinds. The most common species on foodstuffs and faeces are cheese-mites (*Tyroglyphus tiro* and *T. longior*), then the meal mite (*Aleurobius farinae*), and finally the house mite (*Glyciphagus domesticus*), which often occurs on fruit and meat. The evidence of pathogenicity is, however, by no means clear, for while some have thought that large numbers in the alimentary tract are harmless, others consider that they may cause intestinal catarrh and cutaneous eruptions.

The writers have observed dead mites and eggs in human faeces from time to time. Recently, however, they have been of more frequent occurrence, and living eggs have been recovered as well as a female containing an egg ripe for extrusion. These were identified as probably *T. siro*. The patient from whom the specimen was obtained had eaten quantities of over-ripe cheese and suffered from recurrent attacks of diarrhoea, but showed an eosinophilia below 5%. The evidence suggests that this mite is capable of developing in faeces during their passage through the alimentary tract. As far as can be ascertained the presence of mite-eggs in faeces has no pathological significance. No mites have been found in the rationed cheese now being sold in Britain.

LETTER

EFFECTS OF DRINKING SMALL QUANTITIES OF SEA-WATER;
A CORRECTIONTo the Editor, *British Medical Bulletin*

Sir,

My attention has been drawn to an abstract appearing in *British Medical Bulletin* of my communication to the *Lancet* (1944, 2, 441) on "The effects of drinking small quantities of sea-water" The abstract appears on page 236 of Volume 2¹

This abstract does not reproduce the point of my communication, which was that the earlier experiments on drinking sea-water, or of giving sea-water by rectum, had been concerned with large volumes of sea-water, whereas my work was with small quantities which were specified As has also been shown by Elkington & Winkler (*War Medicine*, 1944, 6, 241) the extra salt from sea-water can either be excreted in the urine, in which case the osmotic pressure of the body-fluids is unaffected, or it can be retained with consequent increase in the osmotic pressure, or both may occur to a certain extent The man on shipwreck-rations continues to excrete a considerable amount of urine, because of the diuretic effect of endogenous protein-metabolism, even when in water-debt, this urine is almost chloride-free My experiments showed that this unused chloride-excreting capacity of the kidney could be utilized to excrete the salt contained in small quantities of sea-water, thus using the kidney as a de-salting apparatus

In my original communication I give an expression from which can be calculated the limiting volume of sea-water that can be ingested daily without either calling on the body's water reserves to excrete the excess salt or retaining salt in the body This limiting value is not very high—amounting to about 400 cm³ per day

The point that your reviewer appears to have missed is that I recommend the ingestion of sea-water only up to this limit Even with this small amount of sea-water, there is some increase in urine-volume, but this increase is not so great as the volume of sea-water ingested—hence, there is a small net gain of water to the body amounting to about 100 cm³ per day Though the M R C War Memorandum on The preservation of life at sea after shipwreck does not recommend drinking sea-water, it does suggest that biscuits may be dipped in the sea and that the mouth may be rinsed with sea-water It was considered by the committee responsible for this memorandum that this manoeuvre alone would result in a daily intake of sea-water approaching my limit I am fully in agreement with this

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¹ [BMB 506]

HISTORICAL AND BIBLIOGRAPHICAL NOTES

Antonio De Gimbernat (1734-1816)

Strangely disregarded in medical biography is Antonio de Gimbernat Unmentioned by Arturo Castiglioni or Guthrie, he is recorded by name and date alone by F H Garrison, and receives but a few lines in the encyclopaedic *Handbuch* of Neuburger & Pagel Such are the allusions in some standard works to the man whose name is known to every medical student Yet these omissions concern the anatomist who was Scarpa's rival, the first surgeon of his day in Spain and the man, who—as adviser to the Court entrusted to investigate the claims of Jenner—was instrumental in sending Balmis on the amazing voyage of the *Maria Pita*

When the young Catalan, Pedro Virgili, returned south from Montpellier with the best of anatomical learning, Gimbernat was born in the village of Cambrils The year was 1734 In Tarragona where Virgili learnt the rudiments of surgery, Gimbernat had his schooling His boyhood was spent amid the humblest of surroundings before crossing the Peninsula, as far as he could go, to enrol as a student of medicine in Cadiz The distance was great but there were great attractions—Pedro Virgili and his Real Colegio de Cirugia The school was new and it served the Navy The pre-clinical studies were remarkably like those in Britain physics, chemistry and botany, and then anatomy and physiology At all Gimbernat excelled, but it was anatomy which remained as a relentless hobby in a long and crowded life To the full he justified his favourite and oft-quoted remark "Mi autor más favorito es el cadáver humano" Of his clinical instruction we learn little, but as Virgili himself taught surgery we know that the students were supervised by an exceptional man So wide was the reputation of the Naval School of Surgery of Cadiz, that Virgili was commissioned to found a similar one for the Army, this time in Barcelona, and back to Catalonia he sent his most successful pupil

Gimbernat was 28 years old when he undertook the responsibilities of his first chair—the professorship of anatomy at the Real Colegio de Barcelona It was there that he accurately described the reflexion of the inguinal ligament At the express wish of the King of Spain, Gimbernat was selected in 1774 to go with Mariano Ribas on a visit to the clinics of Paris, and from there to compare French methods with those of England, Scotland and Holland

What delighted him most was the Hunterian approach to the science of surgery, and neither Edinburgh nor the Netherlands seem to have moulded his subsequent career

In 1777 Hunter, then established in Jermyn Street, lectured in his own anatomical theatre After a now historic meeting, Gimbernat informed his teacher of his own dissections and the type of operation he had performed for strangulated femoral herniae On the dissected part he pointed out the curious turn of the inguinal ligament to the pubic bone That attachment was new to Hunter, who acknowledged the fact and referred to it repeatedly later on The name "ligament of Gimbernat" soon became established in London, as it also did in the north of England There William Hey (1736-1819) of Leeds, whose long life so closely corresponds to that of Gimbernat, was quick to note the term It is interesting to observe that the classic, *Nuevo metodo de operar en la hernia crural*, did not appear until 1793

In London, Gimbernat also worked with Hunter at St. George's Hospital and attended the later clinics of Percivall Pott at St Bartholomew's In addition, he found time to study pharmacology under William Saunders, a Scot like Hunter, and like Hunter a fellow of the Royal Society, whose classes in Covent Garden were within easy reach of the Great Windmill Street Anatomical Theatre

Returning to Spain, Gimbernat resumed work in Barcelona, but not for long, as in 1779 he and Ribas were summoned to Madrid to draw up plans for a new medical school Considerable opposition had to be overcome, and it was not until 8 years later that he delivered the opening address at the Real Colegio de Cirugia de San Carlos

Still another task was entrusted to Gimbernat—the establishment of an anatomical and pathological museum Luis Comenge writes that within 6 years the Madrid Museum had no rival in Europe Those who saw in the Royal College of Surgeons of England some exhibits executed under Gimbernat's direction, can well believe the statement It is grievous to record that those perfect specimens of diseases of the eye were lost for ever during the bombing of London on the night of 10 May, 1941

A new era of Spanish medicine followed the foundation of the College of San Carlos where Gimbernat, a man with the confidence of three successive kings, combined the office of director with the chair of operative surgery It was in Madrid that he spent some

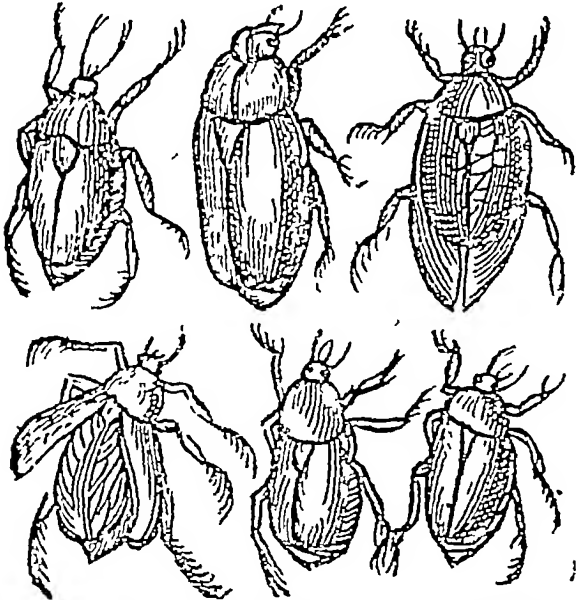
of the most arduous years of his life and it was there that he died at the advanced age of 82 years

Gimbernat was a surgeon in the true sense, his practice was of the widest, as was the custom with the great doctors of the day. He employed gradual compression in the treatment of aneurysms and for years Gimbernat's collyrium " had its place in ophthalmology, as did his classification of corneal ulcers, and his operations for cataract—a disease in which he was particularly interested and from which he suffered so much in his old age. Illustrations of instruments made to his own design tell of his originality, as do his writings. These vary from a paper on the correct use of sutures to articles on medical education and hospital administration. His best known work—"The new method for operating on femoral hernia"—was translated into French, German, and English. Gimbernat knew how to demonstrate his ligament, the beautiful plates in sagittal section make one wonder why, with the advent of anaesthesia, a mid line approach was not described until A K Henry devised the modern operation.

These are a few of the contributions of one of the great masters of medicine in Spain or of any country. As the inspirer of the famous Spanish schools of anatomy his place is secure. Since, however, this pioneer in ophthalmology, vascular surgery, and urology has more than once been described as a herniologist, we must add that it was at the time when that peculiar term put one in good company—with Antonio Scarpa, Peter Camper, Astley Cooper and G J Guthrie

N M Matheson

an apprentice in physick. In the opinion of his contemporaries Muffett's *Silk-wormes* was "no bad piece of poetrie", but it has never achieved the fame of the celebrated didactic poem written on the same subject by Marcus Hieronymus Vida, Bishop of Alba



Cantharides (Spanish fly) This is one of the few figures of medical significance in Muffett.

Dr Thomas Muffett, a Pioneer Entomologist

Thomas Muffett's *Health's improvement* (1655) a gossipy book on diet, is to be found in most of the older medical libraries, and is the work by which its author is now chiefly remembered. It is, however, as a naturalist, and especially as the author of a pioneer treatise on insects, that Muffett has a permanent place in the history of biology.

Thomas Muffett (Moffett, Moufet) was a member of an ancient Scottish family which derived its name from the town of Moffat in Annandale. He was born in 1553, probably in the parish of St. Leonard's, Shoreditch, as the son of Thomas Muffett citizen and haberdasher. After five years at the Merchant Taylors' School he went to Cambridge, where he was a member in turn of Trinity and Caius Colleges. He became a good classical scholar and then studied medicine under Thomas Lorkin and John Caius. After receiving his M.A. degree in 1576 he went abroad. At Basle he attended the lectures of Felix Plater and Theodor Zwinger and, after defending many medical theses, was awarded the M.D. in 1578. In the following year he visited Spain and Italy, where he began to study insects. He paid special attention to the culture of silkworms, and in 1599 published anonymously *The silk-wormes and their flies* lively described in verse by T M, a countrye farmer and

Muffett extended his travels into France, Germany and Switzerland before returning to England. In 1582 he was back at Cambridge and in that year he was incorporated M.D. in his old university. In July 1582 he accompanied Lord Willoughby to Elsinore, to invest King Frederick of Denmark with the Order of the Garter. On this occasion, as he records in his *Health's improvement*, he attended court dinners which lasted from 7 to 8 hours. While on the Continent he became a convert to the teachings of Paracelsus, and one of his earliest publications was a defence of chemical medicines (1584). In the year 1588 when he was elected a fellow and censor of the College of Physicians, he affirmed his orthodoxy by publishing a digest of Hippocrates. He was by this time firmly established in practice and had many distinguished patients including Anne, Duchess of Somerset, widow of the Protector, and Sir Francis Walsingham. In 1591 he acted as physician to the forces in Normandy under the Earl of Essex. He spent much time at Court, and came to know Sir Francis Drake, who first showed him a flying fish. He was patronized by the 2nd Earl of Pembroke, by whose influence he was elected M.P. for Wilton in 1597. The latter part of his life was spent as a pensioner of the Earl, and when he died, on 5 June, 1604, he was buried in Wilton Church.

Muffett's book on insects was completed in 1590 and was partly compiled from the writings of Dr Edward Wotton and Conrad Gesner. Edward Wotton (1492-1555) president of the College of Physicians in 1541-43, was one of the first English physicians to devote himself to the study of natural history. His book *De differentiis animalium* (1552) gave him a European reputation. Muffett also had access to the entomological collections of his lifelong friend Dr Thomas Penny (died 1589). Penny a prebendary of St Pauls, was also a distinguished physician and naturalist. He was a friend of Gesner, Camerarius, Crusius, Lobel and Gerard. His special field of study was botany, but he was also one of the first Englishmen to make a systematic study of insects. In addition to these sources, Muffett had his own collections and notes, the fruits of his many wanderings and of his correspondence with other learned men. He was an accomplished draughtsman and was able to illustrate his own book. Muffett dedicated his book first to Queen Elizabeth, and on her death he wrote a fresh dedication to James I. The work was still unpublished when Muffett died in 1604. The manuscript came into the hands of his apothecary, one Darnell, who sold it to the famous court physician Sir Theodore Mayerne. Mayerne published the work in 1634, in folio, with the title *Insectorum sive minimorum animalium theatrum*. The original manuscript with the two dedications, is still preserved among the Sloane MSS in the British Museum. A translation of Muffett's book, *The theater of insects or lesser living creatures*, was appended to Edward Topsell's *History of four-footed beasts and serpents* (1658). Of Muffett's book it has been said on the highest authority that "both as regards text and figures it is the best work of its kind to its date, and it shows a new standard of exactness in the study of invertebrate animals." 1 Haller denides Muffett's credulity but acknowledges him to be the prince of entomologists before Swammerdam.

Muffett's *Health's improvement* was also a posthumous work. It was probably completed about 1595, but was first edited and published by Christopher Bennett, M.D. in 1655. A new edition, with a short life of Muffett by William Oldys and an introduction by Dr Robert James of 'James's powder' fame appeared in 1746. Muffett himself tells us that he intended to supplement his book of foods by one on drinks, but this work if ever completed, has not survived.

W J Bishop



Title-page of Muffett's *Insectorum sive minimorum animalium theatrum*, 1634

1 Singer, C (1931) *A short history of biology*, Oxford p 95

Robert Hooke (1635-1703)

In a recent paper on Robert Hooke, Mr H W Robinson,¹ librarian of the Royal Society, gives an interesting account of the life and achievements of the great scientist, with special reference to his work in biology and medicine

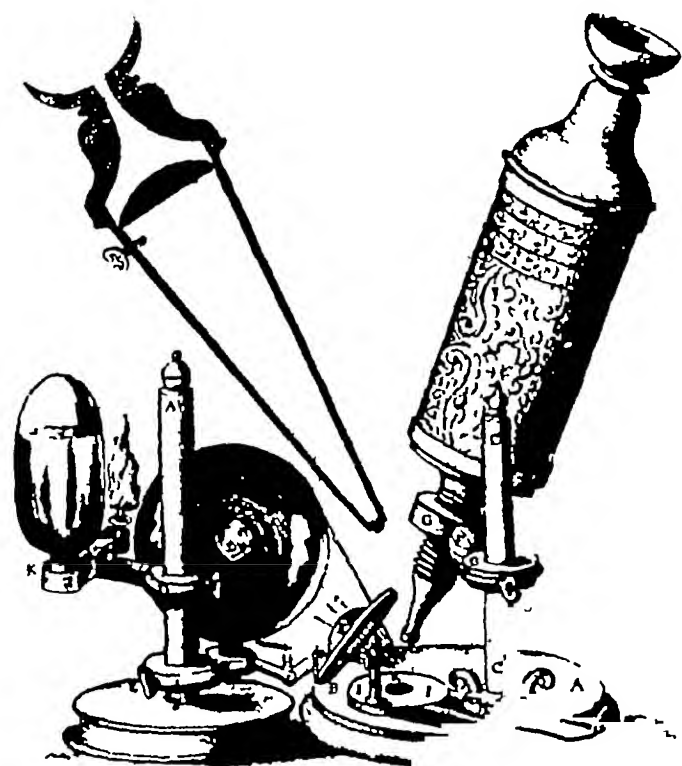
Hooke was born on 18 July, 1635, and was educated at Westminster School and Christ Church, Oxford. He acted for some years as research assistant to Thomas Willis and Robert Boyle. As curator of experiments, and later as secretary, to the Royal Society, he did more than any man to shape the form of the new society and to maintain its existence. He died on 3 March, 1703, and all the fellows of the Royal Society then resident in London attended his funeral.

Hooke claimed more than one hundred inventions, including the anchor escapement, which brought about a revolution in clock-making, a spiral spring to regulate watches, and a universal joint. He introduced freezing-point as zero on the thermometer scale, constructed one of the earliest compound microscopes, made the first Gregorian telescope and a marine barometer, invented a system of telegraphy and assisted Boyle in his work on the air-pump. He was described by John Aubrey as "certainly the greatest mechanick this day in the world". Hooke's *Micrographia* (1665) is the earliest important work on the microscope and the first to give accurate drawings (engraved by the author) made from objects under the microscope. In this book Hooke pointed out the real nature of combustion and made the first reference to cells, which he had observed in cork. Dobell credits Hooke with the discovery of bacteria. His researches and discoveries in astronomy were no less important.

In 1666 Hooke was appointed one of the surveyors for the City of London after the Great Fire and he was principally responsible for rebuilding the capital. He designed the Monument, Bethlehem Royal Hospital, the old College of Physicians in Warwick Lane, and many other important buildings. Apart from his own positive contributions to science, Hooke had an extraordinary insight into the problems with which his successors have had to grapple. One curious example of his prescience, in relation to medicine, is given in the following passage from his *Posthumous works* (1705) in which he anticipates the development of auscultation.

"There may be a possibility," writes Hooke, "of discovering the internal motions and actions of bodies by the sound they make. Who knows but that, as in a watch, we may hear the beating of the balance, and the running of the wheels, and the striking of the hammers, and the grating of the teeth, and multitudes of other noises, who knows, I say, but that it may be possible to discover the motions of the internal parts of bodies, whether animal, vegetable or mineral, by the sound they make, that one may discover the works performed in the several offices and shops of a man's body, and thereby discover what instrument or engine is out of order."

Hooke's time was so engrossed by his official duties that he was unable to follow up his own initial experiments or to make a systematic investigation of any one problem. Many would concur with the judgment of John Robison who described Hooke as "one of the greatest geniuses and most ardent inquirers into the operations of nature." Had Dr Hooke's fortune allowed him to



Two forms of microscope used by Hooke. The simpler, shown in section, consisted of a simple large, plano-convex lens as eyepiece and a very small plano-convex object glass. The conical space within the tube was filled with water. The more elaborate microscope had a tube about six inches long, provided with further draw-tubes by which it could be lengthened. Focusing was brought about by a screw on the nose of the tube. This moved in a ring attached to the stand. The objects, fixed on a pin attached to the base, were examined by reflected light obtained from a lamp to which a spherical condenser was attached (From Singer & Short history of Biology, 1931)

multiply experiments, I make no doubt that he would have stood next to Newton in philosophical rank."

W J Bishop

¹ Robinson, H W (1945) *Proc roy Soc Med* 38, 485

13

Thomas Phaer's Boke of Children (1545)

The first book on diseases of children written by an Englishman was printed 400 years ago and was the work of Dr Thomas Phaer. Phaer's *The Boke of children* was appended to the 1545 edition of his translation of John Bourot's (or Jehan Goeurot's) *Regiment of life*, a popular work on health which derives ultimately from the Salernitan *Regimen sanitatis*.

Phaer (whose name is also spelt Phayre and Phayer) was the son of Thomas Phaer of Norwich. He may have been born in that city, but he lived and died (in 1560) at Kilgerran in Pembrokeshire.

The boke of children.



¶ begyn a treatise
of p cure of childre,
it woulde seme ex-
pedient, & we woulde
declare sonewhat of
the principles, as of
the generacion, the
bering in the wombe,
the tyme of procedynge, the maner of
the byrthe, the byndynge of the nauyl,
lettynge of the members, lawstoppes,
bntions, swathinges, and entreat-
mentes, with the circumstances of
these & many other: which if I woulde
reherse in particuler, it woulde requyre
both a longer tyme, and increase into a
greater volume. But forasmuch as the
most of these thinges are very wyse &
manifest, some pertainynge only to the
office of a midwyfe, other for the reue-
rence

First page of Thomas Phaer's book.

An M D of Oxford, he was also, in accordance with the versatility characteristic of his age, a lawyer and a poet. He wrote a book on legal precedents, and is described as "Sollicitor to the King and Queenes Majesties attending their honorable consaile in the Marches of Wales". His high reputation in his own day and for long afterwards, rested upon his metrical translation of Virgil's *Aeneid*, which first appeared in 1558. Phaer's translation, although second-rate in comparison with Dryden's (1697), was much superior to the work of his two predecessors, the Earl of Surrey and Gavin Douglas. His choice of words is often extremely happy and many later Virgilians have been content to borrow from him. Phaer also wrote original verse and he is no mean representative of the large class of medical poets.

According to Sir Frederic Still,¹ the *Boke of children* is largely copied from graeco-roman writers, while parts are taken bodily from another early English blackletter book, Jonas's translation of Roesslin's *Byrthe of mankinde* (1540). Phaer added little or nothing to the knowledge of children's diseases, but his little book is written in a lively and practical style and he was a pioneer as a writer in the vernacular on the subject.

W J Bishop

¹ Still, G F (1931) *History of paediatrics*, London, p 123

14

Bicentenary of Heberden's Antitheriaca

In 1745, William Heberden, senior, then 35 years of age, published his *Antitheriaca an essay on mithridatum and theriaca*. This sardonic and polished essay is a masterpiece of medical iconoclasm, which offers a brilliant contrast to the uncritical credulity and obscurity of most contemporary references to the same subject. Theriac, the apotheosis of polypharmacy, still enjoyed in the 18th century the unwarranted reputation as a panacea that it had held since the beginning of the Christian era. It was a modification of mithridatum, which was reputed to have been invented as an antidote to all poisons by Mithridates VI (120-36 B.C.), King of Pontus in Asia Minor. Later Andromachus, Nero's physician,

improved upon the original formula by the addition of viper flesh and a number of other ingredients. The improved preparation, which came to be known as *Theriac Andromachi*, ultimately achieved a reputation as a remedy for most human ills. The reputed original formula of Andromachus, which had 63 ingredients, is reproduced by Galen and in most subsequent writings on the materia medica and pharmacopoeias to the 18th century and later. Theriac was publicly prepared in the principal cities of the world, often with great pomp and ceremony, and under the inspection of the Faculty of Medicine, the magistrates, and other important civic officials. So highly was it esteemed, that jars of theriac were considered as suitable presents for emperors. In England, the word theriac became changed to "treacle," which is now the familiar word for molasses. The theriac publicly prepared at Venice, which for long enjoyed a monopoly of the Eastern trade (of which drugs and spices formed a considerable part) came to be held in especial esteem, and theriac was commonly known in England as "Venice treacle." English druggists of the 18th century countered this prejudice in favour of the foreign product by making their own "Venice treacle" and printing the accompanying directions in the Italian language.¹⁰

The "indications" for the use of theriac are too numerous to mention, but it is perhaps worth recording that Louis XIV's apothecary, Moyse Charas,¹¹ recommends it for, among other things, counteracting "the too great effect of purgative medicines and all kinds of super-purgations," a recommendation which awakes recollections of Molière's Monsieur Purgon. Charas may be regarded as an expert on theriac, as he devoted an entire book¹² to the subject, and was also the author of a work¹³ on the medicinal use of the viper.

Many variants of theriac were introduced, and most writers on the subject pressed the claims for their own particular modification. Thus, William Salmon,¹⁴ referring to his *Theriac Londinensis Salmoniana*, says

This is the great Secret with which we cured several hundreds of the Plague in the last great visitation in London, Anno 1665, and to the best of our remembrance not one person died thereof to who we gave it.

The flavour of Heberden's uncompromising denunciation of all this nonsense and superstition is clearly discernible in his opening words

"Mithridates, the famous King of Pontus, had a strange affection of superior skill in the powers of Simples. His Courtiers we may imagine, flattered him upon it, and he has accordingly been delivered down to us as a second Solomon. Whereas if we consider the little leisure, that he had for his own enquiries into this part of nature, or the little helps that he could have from the people about him, we must conclude that his knowledge was very inconsiderable."

What evidence there is, he points out, suggests that the only medicine found in the cabinet of Mithridates after his death was

"a trivial one consisting of twenty leaves of rue, one grain of salt, two nuts, and two dried figs. So that there is some reason to suspect that Mithridates was as much a stranger to his own antidotes, as several eminent Physicians have since been to the medicines that are daily advertised under their names."

Heberden then refers to the "perpetual alarms from an apprehension of poisons" which seems to have been rife in ancient times, and which led to a pre-occupation with the devising of futile antidotes

"What ignorance or an immoderate fondness for life had thus begun, was carried to a much greater height by that strong passion which the Vulgar have ever shown for prodigies and miraculous stories."

In fact, the ancients knew of no poisons "except the Cicutia [hemlock], Aconitum, and those of venomous beasts, and knew no antidote whatever to these poisons."

Theriac, he says, has gradually lost most of the virtues formerly attributed to it, and is now "forced to take refuge in that of a Diaphoretic, which is commonly the virtue of a medicine that has none." Even if we suppose, continues Heberden, that some combination of its many constituents accidentally produced a composition with true antidotal virtues, the specification changes so much from one writer to another "that it has scarce ever continued the same for a hundred years together." However, if "these grand antidotes were only good for nothing," it would hardly be worth while to censure or take any notice of them," but "there are not wanting instances of such ill effects from Mithridatum and Theriaca, as must have been owing to the patient's having more than his share of Opium."

Concluding his argument, Heberden says that he will call supporting testimony from only two authorities, one an ancient writer, Pliny, "who is almost as old as Theriaca", the other a modern writer, Juncker (1679-1759). Pliny is said to have decried "with great vehemence against the injudiciousness, the ostentation and wantonness of this heap of Drugs," and Juncker to have asserted that "Mithridatum and such other medicines have done more mischief in the world than good." Both writers, Heberden adds, "seem, oddly enough to agree in referring the invention of it to the just judgement of heaven, as if the delusion was too strong and unaccountable to proceed from mere human artifice and contrivance." However, in spite of such objections, "it still goes on to be prepared in the old manner in all the great cities of Europe."

Heberden's concluding words deserve reproduction in full

"Enough surely has been given to Antiquity. Let not length of time, which has ever been the fatal enemy of falsehood and imposture, be made in this instance to support and protect them. Perhaps the glory of its first expulsion from a public Dispensary was reserved to these times and to the English Nation. In which all parts of Philosophy have been so much assisted in asserting their freedom from ancient fable and superstition, and whose College of Physicians in particular, hath deservedly had the first reputation in their profession. Among the many eminent services, which the authority of this learned and judicious Body hath done to the practice of Physic, it might not be the least that it had driven out this medley of discordant Simples; which, perhaps, has not better title to the name of Mithridate, than as it so well resembles the numerous, undisciplined forces of a barbarous King, made up of a dissonant crowd collected from different countries, mighty in appearance, but in reality an ineffective multitude, that only hinder one another."

Heberden's words proved to be prophetic, for although theriac was still retained in the London Pharmacopoeia¹⁵ of 1746 it was banished from the succeeding London Pharmacopoeia¹⁶ of 1788, although it remained official in most European countries long after it had become entirely discredited in the British Isles.

The first *Pharmacopoea Germanica* (1872) included a theriac, which had, however, shrunk to only 12 ingredients and omitted viper flesh.

The French Codex¹⁷ of 1837, although edited by a committee which included such distinguished scientific figures as Orfila, Caventou, Pelletier, Robiquet, and Soubeiran, devotes 3 pages to a *thériaque* containing no fewer than 71 ingredients (8 more than in Galen's formula), including dried vipers, and the Codex¹⁸ of 1866 has a *thériaque* of 60 ingredients, among which dried viper is still present. In the Codex¹⁹ of 1884, which remained official until well into the 20th century (1908), the veteran theriac is still retained with 56 ingredients. Although vipers are no longer included, it is still directed that the fresh mixture should be put aside in pots for several months before final pounding in a mortar.

It is interesting to contrast the spirit in which theriac was banished from England in the 18th century, and from France in the 20th. The following passage from the preface of the London Pharmacopoeia²⁰ of 1788 seems to imply almost a feeling of guilt that theriac had remained so long

"Great care has been taken that very few traces should remain of snail superstition. Hence it happens that some prodigious and enormous antidotes, which have really neither bounds nor intention, are at last displaced, — a manifest proof that neither the authority of ancient custom nor reverence of antiquity has any longer too much dominion over us."

On the other hand the following passage from the preface of the French Codex²¹ of 1908 conveys the impression of affectionate regret

"Theriac, which has been retained in modern times only in the Spanish French and Italian pharmacopoeias is today sacrificed. After having held so great and so enduring a place in pharmacy and therapeutics it quits the domain of history to be relegated to that of legend."

N H J

¹ Charas, M. (1668) *Histoire naturelle des animaux, des plantes et des minéraux qui entrent dans la composition de la thériaque d'Andromache*. Paris [Not available, and therefore not consulted, reference taken from *Index catalogue of the library of the Surgeon General's Office, U.S. Army, Washington*].

² Charas, M. (1672) *Nouvelles expériences sur la vipère*. Paris.

³ Charas, M. (1681) *Pharmacopée royale galénique et chymique*. 2nd edition, vol. 1, Paris.

⁴ *Codex medicamentarius pharmacopée française*, 1866. Paris.

⁵ *Codex medicamentarius pharmacopée française*, 1884. Paris.

⁶ *Codex medicamentarius pharmacopée française*, 1908. Paris.

⁷ *Codex pharmacopée française*, 1837. Paris.

⁸ Healde, T. [translated by] & Latham, J. [revised by] (1793) *The pharmacopoeia of the Royal College of Physicians*, 6th edition, London.

⁹ Pemberton, H. [translated by] (1746) *The dispensatory of the Royal College of Physicians*. London.

¹⁰ Quincy, J. (1730) *Pharmacopoeia officialis & extemporanea or a complete English dispensatory*, 8th edition, London.

¹¹ Salmon, W. (1691) *Pharmacopoeia londinensis Or, the new London dispensatory*, 4th edition, London.

A History of Medicine, by Dr Douglas Guthrie

Should a reviewer read the book that he is to review? The question may seem frivolous, but it is not entirely devoid of point. Certainly the reviewer, say, of a large text-book of medicine, is not expected to have read the book in its entirety and, in practice, few scientific or technical books are read from cover to cover for review purposes. What constitutes "reading" by the reviewer is a matter of individual conscience and judgment. It would be interesting to know, for example, the course adopted by the reviewer of such a book as Tidy's *Synopsis of medicine*. For the benefit of non-British readers who do not know this work, it should be explained that it treats the protean manifestations of disease as if they were plants which could be relegated to Natural Orders, with their characteristics presented in tabular form. In fact, the work bears a striking resemblance to a manual of systematic botany (No disparagement of the book is here intended. It is one of a series which is much used by candidates for those exercises in orthodoxy and industry which are sometimes called Higher Professional Examinations, and it has a just reputation for equipping those who have diligently memorized it to give the answers that will be expected of them.)

However, the publication of a new history of medicine in the English language is an exceptional event, and it happens that in this case the reviewer has read the book carefully and in its entirety starting at page 1, and continuing until page 411 (pp. 412-448 are occupied by a bibliography and index). Having adopted this most unusual course, the reviewer is in a state of considerable doubt as to its wisdom. He feels much as if he were called upon to talk entertainingly and with enthusiasm on the subject of food after having just eaten to satiety. How different is the approach to a book which is to be reviewed by the process of random but delicious sampling, which allows the contents to be savoured but does not appreciably diminish the appetite! Nevertheless, a judgment is implicit in the method adopted for it is not without importance to the reader to know that the book can be read from cover to cover—and with pleasure and advantage.

Those who already have some interest in the subject may be curious to know how it compares with other works of medical history in the English language. The two best known English-language works in their respective classes are the *Short history of*

medicine by Professor Charles Singer, who is Britain's most distinguished historian of Science, and the *Introduction to the history of medicine* of the late Fielding H. Garrison.

Singer's book admirably serves the purpose for which it was written—that is, to provide a very brief survey of the growth of medicine as a science. In the author's own words it is "essentially a history of ideas," and as such the narrative is not embarrassed by detail or encumbered by purely biographical or antiquarian material. This book, published in 1928, must already have inspired in many of its readers a wider view of the nature and purpose of medicine and an interest in its history.

Garrison's work is best described as a *Handbuch*, and is the indispensable work of reference in the English language, although, like all works of such magnitude, it is not devoid of minor inaccuracies.

E. T. Withington's *Medical history from the earliest times* was published in 1894 and has been out of print for some years. It is a small but scholarly book and has continued to enjoy a very high reputation, particularly for its treatment of classical medicine.

C. G. Cumston's *Introduction to the history of medicine* (1926) does not go beyond the 18th century. It is interesting for its full discussion of doctrines rather than of discovery and technique, and for its European outlook. It also contains an essay by that most original and stimulating thinker, the late F. G. Crookshank, on "The relation of history and philosophy to medicine."

Guthrie's new history takes the middle course between Singer and Garrison and, because it falls between these two extremes, it is something of a dual-purpose book, which provides a readable narrative (although continuity is necessarily lost in the detail), but is so copiously documented that it is also of more permanent value for reference purposes.

The first 110 pages bring us as far as Salerno, mediaeval medicine is appropriately dismissed in the following 24 pages, and the period from the Renaissance to the end of the 17th century is covered in pages 134–214. The 18th and 19th centuries occupy the next 123 pages, and there is then a departure from the chronological division of matter to separate chapters on military and naval surgery and the conquest of tropical diseases, the rise of specialism and of preventive medicine, journalism, bibliography, and medical history (the 20th and final chapter). The ample bibliographical references are given in the form of (a) numerous footnotes, (b) a list of "Books for further reading" at the end of each chapter, (c) a "Classified bibliography of medical history" as an appendix. The last-mentioned is perhaps the most useful for the novice, because it includes short descriptions of many of the works of medical history listed. The references given as footnotes and those at the end of each chapter should be of particular value to readers of special medical interests who wish for guidance to further literature on the history of their subject. There are no fewer than 72 half-tone plates, including photographs taken by the author at Delphi, Epidaurus, and Cos. The plates are a distinctive and attractive feature of the book, and the author has evidently not spared effort in the search for novel and interesting illustrative material.

The possible criticisms are those that could be made of the first edition of any general history of medicine of more than a certain length: that there are minor inaccuracies, which will diminish in future editions. We refer confidently to future editions, because we feel that this is a book that fills a definite need for an English-language history of medicine of intermediate scope, and that it may well come to be regarded in much of the English-speaking world as a standard textbook on medical history for the general medical reader. (For price and other details see *BMB* 795/167.)

N H J

16

François Magendie (1783–1855)

In writings on medical history from the USA, two extremes are represented. On the one hand there are those works of vulgarization which Ronald Ross stigmatized as "simian journalism" and in which crude and often banal dialogue is "reconstructed" or invented. In contrast, the volume of serious writing on medical history is without parallel in any other country. A recent biography by Prof. J. M. D. Olmsted, *François Magendie, pioneer in experimental physiology and scientific medicine in XIX century France* (New York, 1944), is an example of the latter kind of medico-historical writing. As a physiologist the author is in a position to interpret with authority Magendie's scientific work, which has been the subject of some controversy. He has also undertaken a considerable amount of bibliographical research in obtaining his material from original sources. The result is to present Magendie as a scientist of far greater stature than is commonly accorded to him.

The Bell-Magendie controversy as to priority in the discovery of the distribution of motor and sensory function in the anterior and posterior roots of the spinal nerves is conclusively settled in Magendie's favour, and Olmsted convicts Bell of supporting his case by publishing in 1824 a falsified version of a pamphlet that had originally been printed in 1811. However, Magendie was not always on the side of truth in the vigorous controversies in which he participated. He vehemently denied the contagiousness of cholera, and exhibited an irrational opposition to ether anaesthesia. At a meeting of the Academy of Sciences he produced as his trump card the warning that ether produced erotic hallucinations. "Females thus inebriated had been seen to hurl themselves upon the operator, with gestures and propositions so expressive, that in this singular and novel situation, the danger was not for the patient but for the surgeon." It is not surprising that this ludicrous objection evoked a storm of hilarity.

Magendie's great contributions to medicine were founded upon his spirit of scepticism, leading to a philosophy of extreme scien-

tific empiricism which compares unfavourably with the broader intellectual outlook of his great pupil, Claude Bernard. However, the medical doctrine of his contemporaries was such that Magendie's extremism was probably a necessary antidote.

Olmsted makes a gallant attempt to acquit Magendie of the charge of needless cruelty in his physiological experiments. This attempt is not wholly convincing, and it is difficult to resist the conclusion, in the light of modern psychological concepts, that Magendie's wholesale vivisections for demonstration purposes implied, in those pre-anaesthetic days, a distinct element of sadism. This view is strongly supported, although Olmsted does not draw attention to the point, by Magendie's irrational opposition to surgical anaesthesia.

This is a splendid biography, original in its conception and execution, which should bring great pleasure to all who are interested in the history of scientific medicine. There are a few minor misprints—such as "Dessault," "laudinum."

N H J

17

History of Thermometry The *Ciba Zeitschrift*

Since we published a short note on the history of clinical thermometry (*BMB* 726/1), we have received a number of the *Ciba Zeitschrift* (No. 93, pp. 3288–3328, March 1944) of which the subject is "Das Thermometer." The number is divided into six chapters, all by Dr. R. Vollman of the Institute for veterinary pathology of Zürich University. Dr. Vollman first discusses the early air-thermometers of Galileo, Santorio, Drebbel, and others, and then considers in turn the discovery of the closed thermometer, the standardization of thermometers, the thermometers of Fahrenheit, Réaumur and Celsius, thermometric experiments of medical men, the beginnings of clinical thermometry. There are over thirty accompanying illustrations and a useful list of references, and the whole provides a most interesting and valuable review of the subject.

The *Ciba Zeitschrift* is not as well known as it deserves to be. It is now in its ninth year of publication, and, in normal times, is issued in monthly parts. It is published by a Swiss chemical manufacturing company—the *Gesellschaft für chemische Industrie in Basel*—and is edited by Dr. Karl Reucker with the help of several able assistants. The *Ciba Zeitschrift* has an entirely different character from that of most of the commercial pharmaceutical periodicals. In its matter, it represents a serious contribution to medical history. It is beautifully printed by the firm of Benno Schwabe of Basle, and each number bears ample evidence of the care in the smallest details of production that have been devoted to it by the editor and his staff. The number, selection, and quality of reproduction of the illustrations are outstanding features of this journal.

The *Ciba Zeitschrift* was founded on the initiative of the late Dr. J. Brodbeck-Sandreuter, president of the *Gesellschaft für chemische Industrie in Basel*, who although a lawyer by profession, became interested in, and gave generous support to, the study of the history of medicine. The number of the *Ciba Zeitschrift* to which we referred above contains an obituary notice of Dr. Brodbeck, who died in February 1944, and it is much to be hoped that the journal will long survive its founder as a memorial to his discriminating patronage of medical history.

Ciba Symposia, an associated periodical which sometimes contains translations of the *Ciba Zeitschrift* and sometimes original material, is published in the USA. There is also *Actas Ciba* in the Spanish language, and before the war there was a *Revue Ciba* in French.

N H J

18

THE LIBRARY

Two Important French Surgical Monographs

We have recently received from Messrs. Masson & Cie two new surgical monographs which can hardly fail to be of interest to a considerable number of surgical readers in countries other than France. The first of these is a new work by René Leriche—*Physiologie pathologique et traitement chirurgical des maladies artérielles de la vaso-motricité* (Paris, 1945, 304 pages, 23 figures, 280 francs). This is a sequel to the author's *Physiologie pathologique et la chirurgie des artères*, and in it Leriche discusses vasomotor disorders, surgical and medical, from a physiological and pathological standpoint. Chapters on arterial hypertension and its treatment are included.

The second monograph is a new work on the surgery of the hand—*Chirurgie de la main* (Paris, 1945, 236 pages, 81 figures, 145 francs)—by Marc Iselin. The scope of this work is indicated by the sub-title, *Chirurgie réparatrice des traumatismes de la main*, and it is a companion-volume to the author's previous monograph, of which an English edition was published, on *Chirurgie de la main: plaies, infections et traumatismes fermés de la main* (3rd edition, 1938).

Chemotherapy in France

An interesting number of *La Semaine des Hôpitaux* (1945, 21, 1039–1074) is devoted to chemotherapy, and contains various articles on antibacterial substances of microbic origin (Lachaux), Sulphadiazines in therapy (Varay, Nitti & Cottet), Sulphaguanidine in intestinal infections (Célice), Incompatibilities of sulphonamides (Durel), Experimental basis of chemical therapy of thyrotoxicoses (Bovet, Babinet & Fournel), Aetiology of post-arsenical jaundice (largely a revision of British work.) (Vignalou), Anti-thyroid therapy with aminothiazole (Perrault).

La Semaine des Hôpitaux is one of many French journals which have in recent months made a welcome re-appearance in Britain.

Medical Documents at Geneva

The Swiss journal *Médecine et Hygiène* (1/12/44) contains an article by M. André Blum, curator of the Musée du Louvre, on some early medical documents in the Bibliothèque publique et universitaire de Genève. Reference is made to a thirteenth-century MS. containing translations of some of the works of Rhazes and Alexander of Tralles, and to an incunabula, *De viribus herbarum*, attributed to "Macer Floridus". A woodcut from the Macer Floridus is reproduced.

Paracelsus

Three years ago the fourth centenary of the death of Paracelsus was celebrated in Switzerland. A Swiss Paracelsus Society (Schweizerische Paracelsus Gesellschaft) was formed, and the publication of a journal, *Nova Acta Paracelsica*, was commenced.

In addition, the first of a series of selections from the works of Paracelsus has been published under the title *Paracelsus, der Mediziner und Kulturhistoriker* (Zollikofer, St. Gall). The titles of 3 further volumes are announced (*Médecine et Hygiène*, 1/2/45).

New British Medical Quarterlies

In 1946 the British Medical Association is to publish three new special quarterly journals: the *British Journal of Pharmacology and Chemotherapy*, the *British Journal of Social Medicine and Thorax*. The first is to be published in co-operation with the British Pharmacological Society, and the third with the Association for the Study of Diseases of the Chest. The proposal for publishing the second journal came from Professor F. A. C. Crew, Professor Lancelot Hogben and Sir John Orr. Discussions for launching these new periodicals have been going on for the past two years, but it is only now that paper supplies have made possible the commencement of publication.

New Spanish Journals

Revista Española de Fisiología (Barcelona). The 2nd number of vol. 1 of this journal appeared in June 1945. It contains 5 original papers, all of them with summaries in Spanish, English and German, a review article—*Modernos conceptos sobre histofisiología de la médula ósea*, and a book review section. The journal is published under the auspices of the Consejo Superior de Investigaciones Científicas.

Revista Española de Cirugía (Madrid). The first four numbers of vol. 1 of this monthly journal have been received. The journal is

well produced and illustrated. Each number contains four to eight signed papers, a comprehensive abstracting section, and book-reviews. Most contributors are Spanish, but there are also papers by one Argentine and two German authors. The first number includes an interesting article by M. Ortiz Picon on *La Técnica Microquirúrgica*.

Revista Española de Pediatría (Zaragoza). The fourth number of vol. 1 has recently been received. It contains seven signed articles and ample abstracting and book review sections.

Acta Pediatrica (Madrid). This is a monthly journal which is now in its third year of publication. The numbers for April, May, and July of 1945 have recently been received.

Revista Española de Cirugía, Traumatología y Ortopedia (Valencia). This journal, now in its second year of publication, reflects the growing importance in all countries of the surgery of bones and joints. It is produced by the publishers of *Medicina Española*, and is well printed and illustrated.

Other Books Received

Tratamiento pre y postoperatorio (Salvat Editores, S. A., Barcelona) by Dr. F. Domenech Alsina, late assistant professor of surgical pathology in the University of Barcelona, and Dr. J. Pi Figueras, surgeon to the Hospital de la Santa Cruz y San Pablo, appears at a time when considerable advances have been made in therapeutics and includes methods of treatment which have not hitherto been examined in detail in any text book. Chapters are devoted to the treatment of dehydration, proteinaemia and shock, to the pre- and post-operative uses of vitamins of blood transfusion and of chemotherapy (sulphonamides, penicillin), to the treatment of diabetic patients, to pre-anaesthetic medication and to a wide range of post-operative complications and the special measures necessary to deal with each.

Quelques vérités premières sur la transfusion sanguine (Masson, Paris, 1945) by A. Tzanck and M. Bessis, is a collection of aphorisms, divided into six chapters, on blood transfusion. One of the aphorisms (p. 25) in the chapter on transfusion in traumatic shock is very much in accord with views recently expressed by the Medical Research Council: "L'appellation de choc n'a pas aujourd'hui plus de précision que jadis celle de fièvre. C'est à distinguer avec précision les différentes sortes de chocs que doivent porter tous nos efforts." It is strange to find in the chapter on blood-groups no mention of the Rh factor, and this emphasizes the divorce during the war of Continental and Anglo-American medicine.

795

BOOKS

[The prices quoted are those which obtain within the United Kingdom. Editors of medical journals who wish to review publications of which notices appear below are invited to apply to the Editor for review copies, of which a few are sometimes available. Orders for any of the publications mentioned below may be sent to the Editor if there are difficulties in obtaining them locally.]

Publications may be referred to by the numbers given at the left of each item, e.g. Book 167. It should be noted that supplies of all publications are limited and there can be no certainty that publications ordered or requested for review will be available. Publications are arranged according to the Universal Decimal Classification and the classification number of each publication is given at the right.]

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A HISTORY OF MEDICINE

by Douglas Guthrie. London, Thomas Nelson and Sons Ltd., 1945. 448 pages, 72 plates. 22 x 15 cm. £1 10s. [£1.5]

[See BMB 794/15 for review]

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devoted to tissue metabolism, gastric secretion, the use of tracer isotopes and lymph.

A new feature, which it is hoped will remain in future editions, is a short historical note which prefaces each section.

It is to be regretted that an account of some of the recent work on man, for example in respect of haemorrhage, the life of the erythrocyte, the absence in the diet of certain specific substances, have escaped inclusion. Nevertheless, this edition will worthily maintain the reputation of both book and author.

In closing, mention must be made that the book has been completely reset and fully upholds the high standard set by its publishers.

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PRINCIPLES OF HUMAN PHYSIOLOGY

originally written by E. H. Starling. Ninth edition by C. Lovatt Evans, the Chapters on the Special Senses by H. Hartridge. London, J. & A. Churchill Ltd., 1945. x + 1155 pages, 668 illustrations. 25 x 15 cm. £1 16s. [£1.8]

The appearance of the ninth edition of Starling's *Principles of human physiology* will be welcomed by English speaking physiologists. No other physiological text has matched it in its thirty-three years' existence. This edition retains the basic structure of the original and previous editions. It has 268 fewer pages than the first edition, although every section is well abreast of contemporary developments. In spite of the condensation which has had to be employed, the text is lucid and one is impressed by the aptness with which the selected material has been collated. The text is reasonably documented throughout with footnotes and each section closes with a list of carefully selected references.

The book consists of eight sections. The first deals with structural biochemical and biophysical principles. This is followed by an account of the tissues subserving movement and conduction. The third section is an account of the central nervous system. The fourth, which is allocated to the special senses, has been written by Professor H. Hartridge and contains a new essay of the merits of the triple cone theory of colour vision. Blood, circulation and respiration form the fifth part, and are followed by sections on excretion and temperature regulation and, finally, the endocrine and reproductive systems.

The chapter on temperature and heat balance in the body has been entirely re-written. Elsewhere numerous alterations and additions have been made to bring the text into line with our advancing knowledge, mention may be made of the paragraphs

612 (02)

612 (02)

APPLIED PHYSIOLOGY

by Samson Wright. Eighth edition. London, Oxford University Press, 1945. xxx + 944 pages, 513 illustrations. 22 x 14 cm. £1 10s. [£1.5]

A book which has seen eight editions and eight reprintings within twenty years clearly needs no advocate. As a reviewer of the first edition foresaw, Dr. Samson Wright's *Applied physiology* meets a real need for it correlates the preclinical subjects with clinical work and for this purpose revision classes in physiology in its practical application are of great value to men working in the wards and outpatient departments to which one might also add and men in general practice.

In the latest edition the author has radically revised the greater part of the text in order to incorporate a superb selection of the development of human physiology in the past decade.

Although the war has delayed the progress of much fundamental research, investigators have had to apply themselves to the solution of many problems which are particularly concerned with human physiological adaptation. Not all of this work has as yet become available but much of what has been published is of fundamental importance and has been skilfully collated in the text. Particular attention has been given to haemorrhage, blood transfusion, traumatic shock, anoxia, the effects of altitude and climatic conditions, and nutrition. Some six and a half pages have been devoted to an analysis of the British war rationing system, a survey

which fully endorses the author's conclusion that "the British people have been better rather than worse fed during the war, thanks to the wise application of scientific knowledge to the solution of the problem."

Finally, this edition is noteworthy for its extensive use of illustrations. In a text of 893 pages, 513 illustrations have been used. In order to help those who are less familiar with the interpretation of physiological figures, the author has added an appendix in which he has made a critical analysis of two figures. Most readers, if not all, might profitably begin with the appendix.

For the senior student of physiology, the clinical student, all doctors and physiologists, this book continues to be a unique repository of information, particularly in regard to man.

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MANUAL OF NUTRITION

612.39

by R Simmonds London, Cassell & Co, Ltd, 1945 90 pages
14 x 11 cm 1s [£0 05]

This booklet, one of the manuals produced by the British Red Cross Society for the use of its members, has been written by the dietitian to the Hammersmith Hospital (London County Council) and British Postgraduate Medical School. It sets out the fundamentals of the science of nutrition, together with explanations of technical terms. A useful feature is the inclusion of a table showing the nutritive values of various foodstuffs.

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615 1-083

AIDS TO MATERIA MEDICA FOR NURSES

by A E A Squibbs Second edition London, Baillière, Tindall & Cox, 1944 196 pages 16 x 10 cm 4s [£0 2]

In this book each system of the body is considered in turn in relation to the drugs which affect it. In the new edition the chapters on specific drugs and vitamins have been rewritten and a table of doses and drugs in common use has been added. The book covers the materia medica examination syllabus of the General Nursing Council, and includes examples of typical questions set in the recent examination papers of the council. The author is sister tutor to the General Infirmary, Leeds, and an examiner to the General Nursing Council for England and Wales.

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615 82

MASSAGE AND MEDICAL GYMNASTICS

by Mary V Lace Third edition London, J & A Churchill Ltd, 1945 xi + 244 pages, 126 illustrations 20 x 13 cm
12s 6d [£0 625]

The appearance of this well-known manual in its third edition will be welcomed by all physiotherapists and gymnasts, many of whom, as students, profited by its clear presentation of the fundamental principles of exercise-therapy and massage. Rehabilitation by patients' own active endeavours, assisted and supervised by trained personnel, is applied far more widely now than when Miss Lace's book first appeared ten years ago, it is thus more topical than ever.

The physiological basis for exercises is discussed, and the purpose of each group of movements is made clear. The indications for and against the prescription of muscle-work are given due consideration. Descriptions in the text supplemented by clear line-drawings show the different starting positions and how each exercise is carried out. The various types of movement possible are explained, the muscles involved at each exercise being indicated throughout. Particular attention is naturally paid to the active correction of postural deformity.

Manual technique is dealt with concisely. The diverse ways in which the masseuse uses her hands, and her purposes in doing so, are explained with due reference to the physiological effects of each method. Balance is displayed throughout, no more than is justified being claimed for each type of manual treatment.

One question inevitably arises in the mind of all reviewers of this type of book: to what extent does the subject matter keep close touch with present-day practice? At how many schools or rehabilitation centres are some of the exercises described here ordered with sufficient frequency to justify their inclusion in a student's text-book? By contrast, how many simple exercises in everyday use in remedial work are omitted? In a book of this sort, stress is rightly laid on fundamentals rather than their detailed application, nevertheless, teaching is most easily assimilated by students when they are able to follow it up by immediate daily practice on patients. Here the gap is wide in places. Though to-day's methods are all derived from the fundamental work so well set out in this manual, the provision of material closer in form to present-day measures would greatly ease students' tasks. Miss Lace's talent for succinct exposition and clear thought makes one hope that it is she who will take the steps to fill this hiatus.

Contents Part I Massage Part II, Medical gymnastics theory of movements, starting positions, leg movements, arm movements, head and neck movements, passive trunk movements, back movements, abdominal movements, respiratory movements, special scoliosis movements.

173

615.83

OUTLINES OF PHYSICAL METHODS IN MEDICINE

by G D Kersley London, William Heinemann (Medical Books) Ltd, 1945 85 pages, 4 plates. 19 x 12 cm 6s [£0.3]

This small book runs succinctly over the whole field of physical methods of treatment, outlining for the interested practitioner the

different measures at his disposal. The broad view afforded, and the author's explicit prose, could hardly be improved upon.

The principles underlying the construction of each type of electrotherapeutic apparatus are clearly set out. The nature of the currents and rays emanating from them are described and the physiological effects of each explained. Care is taken not to claim too much for electrotherapy in rheumatic disease, while its value in septic conditions, is, if anything, understated. The well established method of ionization with sulphonamide compounds, and its newer application to penicillin, are not mentioned. The disorders calling for electrical methods—faradism, galvanism with and without drugs, heat in its various forms and ultra-violet irradiation—are listed, even x-ray therapy is mentioned. The action of hydrotherapy is explained together with its techniques, indications and dangers. Balanced judgment is maintained throughout, the author is obviously master of his subject.

The touch is less sure in the sections devoted to remedial exercises and manual methods. Stress is laid on the wide usefulness of exercise-therapy and its separate application to invalids and to the merely untrained distinguished. Postural deformity is considered briefly, the post-operative treatment of hernia is set out in detail, breathing and puerperal exercises are dealt with rather cursorily. Massage is dismissed in three pages, manipulation receives bare occasional mention. The action of muscles is not always correctly ascribed and indications and contra-indications are no longer given prominence. Some exercises for some parts of the body are detailed, but the subject matter is dealt with unevenly. Lewis's work on referred pain is ignored and the obsolete idea repeated of "fibrositis" pressing on a nerve. These, however, are minor blemishes in a book so successfully designed to present a concise review of methods of physical treatment rather than the conditions to which they are applicable. Nevertheless, this divorce is essentially artificial and remote from the proper practice of physical medicine.

Doctors faced with numerous patients suffering from the different disorders included within the term "rheumatic" will welcome this booklet for the summary of physiotherapeutic methods that its pages offer. Many medical men will be rightly attracted by its small compass and pleasant style. It may thus prove that such a publication as this will be more widely read and therefore prove more generally useful than the fuller dissertation of which the author is obviously capable.

Chapter headings (i) introduction, the scope of physical medicine, physical fitness (ii) electrotherapy, (iii) heliotherapy, (iv) Roentgen and radiotherapy, (v) movement and principles of remedial exercise, (vi) massage, (vii) hydrotherapy, (viii) occupational therapy.

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THE RHEUMATIC DISEASES

616-002 77

by G D Kersley Second edition London, William Heinemann (Medical Books) Ltd, 1945 120 pages, 40 illustrations 22 x 14 cm 15s [£0 75]

Since the first edition of this book in 1934, our knowledge of the nature of the rheumatic diseases has made little progress. This second edition records what new advances have been made, but its most valuable aspect, from the point of view of the general practitioner and senior student (for whom it is mainly intended), is the emphasis it gives to the practical application of what little knowledge we do possess. As Sir Francis Fraser points out in his introduction, this is largely the result of our wartime experiences of rheumatic disabilities and their most efficient treatment.

A chapter has been included dealing with the aetiology and inter-relationships of the rheumatic diseases, this could with advantage, in so short a book, be more dogmatic and less discursive. Phrases such as "autonomic irritability," "endocrine imbalance," "fringensensitivity," and "metabolic dyscrasia" are merely ornamental cloaks for ignorance, cloaks perhaps hallowed by tradition, but out of place over a "utility" suit.

The chapters on treatment are excellent—a nice balance being kept between enthusiasm and scepticism. Particularly useful is the succinct account of physiotherapeutic measures, and the illustrations of these. The skiagrams, with the exception of the dental films, are so poorly reproduced as to be almost worthless.

The references give a good survey of English work—over half of them are from journals published in Britain.

Chapter headings (i) introduction, (ii) the rheumatic diseases, their aetiology and inter-relationship, (iii) rheumatic fever, (iv) rheumatoid arthritis, Still's disease and climacteric arthritis, (v) specific infective arthritis, (vi) conditions simulating arthritis, (vii) osteo-arthritis (viii) spondylitis, (ix) gout, (x) fibrositis, (xi) sciatic pain, (xii) special treatments.

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616-006

KETTLE'S PATHOLOGY OF TUMOURS

by W G Barnard & A H T Robb-Smith. Third edition London, H K Lewis & Co Ltd, 1945 viii + 318 pages, 191 illustrations 22 x 14 cm £1 1s [£1 05]

The first edition of Kettle's *Pathology of tumours* was published in 1916, the second in 1925. Now a third edition makes its appearance, 20 years after the last and 9 years after the lamented death of the original author. Edgar Hartley Kettle was held in high regard by his brother pathologists in Britain. His wide and accurate knowledge of his subject, technical skill and sound judgment placed him in the front rank of his contemporaries, while his keen wit, friendliness and sociability assured him of a warm place in their affections. As with so many of our best cancer research workers, his special studies in this field were broad—based on a full

and intimate knowledge of pathological principles. It is wholly fitting, therefore, that Professor Barnard and Dr Robb-Smith should "humbly dedicate" their new edition "to the memory of a great teacher and valued friend" and should consider their efforts amply repaid, if as a result of its publication, Kettle's name is kept fresh in the minds of students of pathology.

"In the years that have passed since the publication of the second edition great advances have been made both in the experimental and in the detailed histological studies of tumours" and the authors have included in the new edition those they think most likely to form permanent additions to knowledge, while at the same time trying to "preserve as much as possible the character and happy phraseology of the earlier editions." As in them, the subject matter is divided into three sections—the general biology, general pathology and special pathology of tumours occupying 66, 140 and 99 pages respectively, with 13 pages of index. Naturally a good deal of the old text still remains, but in places there are extensive alterations and additions. Most of the figures are still Kettle's original (and admirable) drawings. To these have been added a few well-chosen photographs and photomicrographs. There is no bibliography, but over a hundred references most of them to recent British and American literature, are provided as footnotes to the text.

Coming down to details we find a new short account of occupational cancer, with a useful table showing in parallel columns the various forms of occupational cancer in man and their experimental counterparts, where such exist. In the section on classification it is pleasing to find that Adami's embryological classification is still given in full. It may be that it is "scarcely suitable for everyday use" but we wholly agree with the authors that it is "more scientific and suggestive than any other with which we are acquainted." The section on reticulosarcoma and lymphosarcoma is good and commendably brief, but marred by disorientation of all five figures and the misnumbering of Figs. 31 and 32 on p. 111. The section on tumours of the ovary has also been brought up to date and there is a much enlarged section on tumours of nervous tissues, including many useful new figures.

There is now so much detailed information available about tumours that it must be exceedingly difficult for writers of small manuals like "Kettle" to decide just what to include and what to omit. The fact of the matter is that the special pathology of tumours does not readily lend itself to summary treatment. If a book on this subject is to be of any real value, rare as well as common tumours must be adequately described. In the present volume the authors have wisely concentrated on the more important and more interesting tumours for fuller treatment, many of the others being merely mentioned.

It is regrettable that so many printer's errors have escaped correction, many of them of the most flagrant description. The book otherwise is well produced. It is eminently readable and should prove a useful accessory to the students' manual of pathology.

Contents. I. The general biology of tumours: definition, structure, growth, innocency and malignancy, multiple tumours, retrograde changes, dissemination, aetiology, the experimental study of cancer. II. The general pathology of tumours: terminology and classification; the innocent connective tissue tumours, the carcinomata, tumours of nervous tissue, tumours of the central nervous system, tumours of the sympathetic system, tumours of the nervous sheaths and peripheral nerves, the melanomata, the endotheliomata, the teratomata. III. The special pathology of tumours: tumours of the skin and subcutaneous tissues, tumours of muscles and fasciae, tendons and bursae, tumours of the bones, tumours of the circulatory system, tumours of the respiratory system, tumours of the alimentary system, tumours of the nervous system, tumours of the urinary system, tumours of the male genital organs, tumours of the female genital organs, tumours of the breast, tumours of the ductless glands.

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IMPERIAL CANCER RESEARCH FUND

Forty-second annual report, 1944-1945. Published by the Imperial Cancer Research Fund, Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, 1945. 25 x 18 cm. 24 pages.

This report was presented to the annual general meeting of the governors on 18 April, 1945, by the director, Dr W. E. Gye.

Induction of tumours with pure chemical substances. Mr H. G. Crabtree, continuing his work of the previous year, which has now been published, has provided evidence, both chemical and biological, that a variety of substances which specifically lower sulphur metabolism in cells cause a retardation (or under chosen conditions, a reversal) of the carcinogenic action of 3,4-benzpyrene and 1,2,5,6-dibenzanthracene. A number of other substances known to interfere with other specialized metabolic processes has been shown to have a negligible influence on the initial stages of carcinogenesis, thus emphasizing the important part played by sulphur metabolism in the mode of action of carcinogens.

Following up the work of MacKenzie and Rous, which disclosed latent neoplastic changes in tarred skin in rabbits, Dr B. D. Pullinger has continued to work on the stimulating effect of wound healing on tumour development in mice, and has studied the question of refractoriness towards tumour development. The results achieved suggested that multiple injuries are more effective in mice than a single one in overcoming latency of neoplasia or cell-refractoriness, and that repeated excision of tumours at the same site might result in a number of localized tumours significantly greater than that due to chance alone. Evidence was found that pointed to an essential resistance in certain individuals which precludes the occurrence of any undisclosed latent neoplastic change. It also appeared that a highly active carcinogen not only caused

more individuals to bear tumours, but it also overcame resistance towards latent neoplastic change.

Sarcomatous transformation of the stroma of mammary cancers. Dr R. J. Ludford and Miss H. Barlow are conducting a series of experiments on mice to elucidate the factors concerned in sarcomatous transformation and have extended their investigation to the behaviour of lung tumours in tissue cultures. The results so far reached emphasize the significance of the stimulation of fibroblastic growth by the carcinoma cells and the survival of stromal cells after transplantation owing to their being of the same genetic constitution as the cells of their new hosts.

Mammary cancer. Dr L. Dmochowski has continued his experiments on mammary cancer in inbred strains of mice. He has found that the milk factor can be transmitted through mice of different genetic constitutions and give rise to breast cancer in mice of a still different genetic constitution and that the milk factor derived from any high-cancer strain of mice can induce breast cancer in susceptible strains of mice, although their genetic constitution differs from that of the strain from which the milk factor originated. It was found possible to induce a comparatively high incidence of breast cancer in a low-cancer strain of mice by administering the milk factor to their mothers, which do not themselves develop breast cancer. Bittner concluded that the milk factor has to be present from the time the mammary glands begin to develop in order to prepare for the cancerous change, but Dr Dmochowski has shown that a high incidence of mammary cancer can be induced in older female mice in which the mammary glands have completed their development in the absence of milk factor, though older mice require approximately twelve times as much milk factor as the younger mice in order to give a similar tumour-incidence. Dr Dmochowski has also continued investigations on the action of stilboestrol on prostate tumours in mice. He has found that when it is applied at the time of tumour transplantation, the growth of tumours is retarded or completely inhibited, but that it has no effect when given after a palpable tumour growth has appeared.

Hormones. Dr E. Vazquez-Lopez has continued work on the pituitary gland. Tumour-like enlargements, of a purely hyperplastic nature, of the anterior lobe have been produced in mice and rats by oestrogen treatment. A more moderate enlargement was obtained by administration of thiourea. Experiments in rats in combined treatment with thiourea and stilboestrol are still in progress. In at least one of the rats growth was able to invade the brain extensively, and a remarkable abundance of acidophil cells has been produced in the growth, but it is too soon to assume the true malignant character of these tumours.

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616-053.22

THE PREMATURE BABY

by V. M. Crosse. London, J. & A. Churchill, 1945. 156 pages, 14 illustrations. 20 x 13 cm. 10s. 6d. [£0.525]

The declining population and low birth rate in Britain have caused more attention to be paid to the prevention of early loss of life of which the greatest single cause is prematurity. The reduction of the mortality due to prematurity can be brought about by (i) the prevention of premature labour and (ii) the care of the premature infant. In 1931 a unit for the care of premature babies was opened in Birmingham, and the author of this work, as chief obstetric officer in charge of this unit, has been responsible for the care of 2,575 premature babies during the years 1931-43. The experience gained during that period has been recorded in the book. Particular attention has been given to the reduction of mortality amongst premature infants, which has been achieved by the application of carefully planned schemes of management and feeding. In addition, practical methods are described which can be employed in the care of the infant at home.

Chapter headings: (i) definition and characteristics, (ii) general scheme of management and care, (iii) institutional care, (iv) home care, (v) clothing, (vi) methods of feeding, (vii) complications liable to occur in the premature baby, (viii) statistics in relation to the premature baby.

616-07

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AN INDEX OF DIAGNOSIS OF MAIN SYMPTOMS

by various writers. Edited by Herbert French, assisted by Arthur H. Douthwaite. Sixth edition. Bristol, John Wright & Sons, Ltd., 1945. 1128 pages, 798 illustrations. 25 x 16 cm. £4 4s. [£4.2]

A new edition of "French" has been long in demand and the present edition, published under particularly difficult conditions, will be most welcome, for the book has, during the past 30 years, gained a great reputation in Britain as the standard work on differential diagnosis.

It covers the whole ground of medicine, surgery, gynaecology, ophthalmology, dermatology and neurology. The book is an index in the sense that its articles on the various symptoms are arranged in alphabetical order, it discusses the methods of distinguishing between the various diseases in which each individual symptom may be observed. The general index at the end of the book gathers these symptoms together under the headings of the various diseases. The text has been carefully revised to include new laboratory tests and diagnostic methods. The book is profusely illustrated, many of the illustrations being in colour. The editors are respectively consulting physician and physician to Guy's Hospital.

List of contributors: Sir E. Farquhar Buzzard, S. E. Dore, A. H. Douthwaite, R. W. B. Ellis, J. W. H. Eyre, Herbert French, Sir William Hale-White, Sir Arthur Hurst, Sir Robert Hutchison.

AIDS TO FEVERS FOR NURSES

by J M Watson. Second edition London, Baillière, Tindall & Cox, 1945 362 pages; 35 illustrations 16 x 10 cm 4s [£0.2]

This book is intended to help student nurses during their training in the nursing of infectious diseases. The introductory chapters are devoted to the first part of the General Nursing Council's syllabus, succeeding chapters deal with specific infections and their management, and the work thus forms a complete textbook for those taking the British State examination on the subject. In this second edition the text has been revised and enlarged.

A TEXTBOOK OF SURGICAL PATHOLOGY

by C. F. W. Illingworth & B. M. Dick Fifth edition London, J & A. Churchill, Ltd, 1945 728 pages, 306 illustrations 23 x 15 cm £2.2s [£2.1]

This book, which first appeared in 1932, has proved its value to senior students and graduates in medicine, for whom it was designed to provide an account of the pathology of surgical diseases. In this new edition, the sections on surgical shock and burns have been rewritten and incorporated in a new chapter on the constitutional effects of injury. The section on anaerobic infections of wounds has been revised in accordance with experience gained during the war. A number of new subjects have been included, chief of which are the crush syndrome, Boeck's sarcoidosis, argentaffine tumours of the intestine, and interstitial-cell tumour of the testis. Several changes have been made in the illustrations. This work provides a most valuable description of those aspects of surgical disease that are outside the scope of a text-book of general pathology. Professor Illingworth is Regius professor of surgery, University of Glasgow, and Mr Dick is surgeon for diseases of the chest, Emergency Medical Service.

(i) inflammation, (ii) wound infections, (iii) constitutional effects of injury; (iv) tuberculosis, (v) actinomycosis, (vi) Hydatid disease, (vii) tumours, (viii) diseases of bones, (ix) diseases of joints, (x) diseases of muscles, tendon sheaths and bursae, (xi) diseases of blood vessels, (xii) diseases of lymph glands and vessels, (xiii) diseases of the skull and brain, (xiv) diseases of the spine and spinal cord, (xv) diseases of the peripheral nerves, (xvi) diseases of the thorax, (xvii) diseases of the breast, (xviii) diseases of the mouth, jaws, salivary glands and neck, (xix) diseases of the thyroid gland, (xx) diseases of the parathyroid glands, (xxi) diseases of the pharynx, larynx and oesophagus, (xxii) diseases of the stomach and duodenum, (xxiii) diseases of the small intestine, (xxiv) diseases of the colon, (xxv) diseases of the vermiform appendix, (xxvi) diseases of the gall-bladder, liver and bile ducts, (xxvii) diseases of the peritoneum, (xxviii) diseases of the pancreas, (xxix) diseases of the spleen, (xxx) diseases of the adrenal glands, (xxxi) diseases of the urinary organs, (xxxii) diseases of the male generative organs, (xxxiii) diseases of the female generative organs.

PSYCHOLOGY IN GENERAL PRACTICE

edited by A. Moncrieff London, Eyre & Spottiswoode (Publishers) Ltd., 1945 199 pages 22 x 14 cm 12s 6d [£0.625]

This new volume in the *Practitioner Handbooks* series brings together 16 authoritative articles, the majority of which have been previously published in the *Practitioner*, and it is designed for general practitioners who have no specialized knowledge of medical psychology. Chapters specially written for this book are "Sex problems," by E. F. Griffith, "Mild depressive psychoses," by C. H. Rogerson, and an appendix by S. R. Tattersall on "Procedure for mental hospital admission and discharge." The remaining chapters have been revised by their authors and brought up to date where necessary. The various sections have been blended into a useful volume under the careful editorship of A. Moncrieff, and a full index is provided.

Contents (i) introduction, the attitude of the general practitioner (M. Culpin), (ii) classification and methods of case-taking (A. S. Paterson), (iii) Differential diagnosis of psychological illness (R. D. Gillespie), (iv) general principles of treatment (H. Wilson), (v) mild-depressive (affective) psychosis (C. H. Rogerson), (vi) anxiety states (T. M. Ling), (vii) obsessions and compulsive states (A. H. Boyle), (viii) hysteria (T. J. Hennelly), (ix) visceral neurosis (C. H. Rogerson), (x) psychosomatic medicine and the rheumatism problem (J. Halliday), (xi) problems in childhood, part I (A. Maberly), (xii) problems in childhood, part II (D. R. MacCalman), (xiii) minor degrees of mental defect (D. R. MacCalman), (xiv) delinquency (D. Curran), (xv) psychiatric social work (K. Edkins), (xvi) sex problems (E. F. Griffith).

AIDS TO PSYCHIATRY

by W. S. Dawson Fifth edition London, Baillière, Tindall & Cox, 1944 306 pages. 16 x 10 cm. 6s [£0.3]

This short introduction to the subject, written by the professor of psychiatry, University of Sydney, has undergone extensive revision in the present edition. It contains chapters on (i) psychology, (ii) psycho-pathology, (iii) causation of mental disorders, (iv) classification of mental disorders, (v) theories of the psychoneuroses, (vi) neurasthenia and nervous exhaustion, (vii) anxiety states, (viii) hysteria, (ix) obsession, (x) psychoneurosis in war, (xi) sexual perversions and anomalies of the sexual instinct, (xii) manic-depressive psychosis, (xiii) schizophrenia, (xiv) paranoid states, (xv) toxic psychoses, (xvi) alcoholism, (xvii) general paralysis, (xviii) epilepsy, (xix) dementia, (xx) mental disorders associated with physical diseases, (xxi) differential diagnosis of certain mental states, (xxii) mental deficiency (amentia) (oligophrenia), (xxiii) treatment, (xxiv) legal aspects of insanity, (xxv) case-taking, (xxvi) mental hygiene.

EXTENSILE EXPOSURE APPLIED TO LIMB SURGERY

by Arnold K. Henry Edinburgh, E. & S. Livingstone Ltd., 1945 180 pages, 127 illustrations 25 x 17 cm £1.10s [£1.5]

In this book, written with the unique clarity and elegance for which he is famous, Professor Henry describes a series of operative exposures in the limbs which are extensile in range so that they may be rapidly and easily enlarged when required. The groundwork has been previously laid down in the same author's *Exposure of long bones and other surgical methods* (Wright & Sons, Bristol, 1927), and the keynote is a uniform simplicity in the unveiling of the part which allows "exposure" to attain its real meaning, quite distinct from any struggle to break through a concealing superficies. The standard approaches utilize the basic anatomy of the limbs, described in homely similes, and the two best known are the anterior exposures of humerus and femur, easily extensile to hip and knee, or shoulder and elbow joints. But many other ingeniously contrived devices are shown, such as the unroofing of the deep gluteal structures, or the approach to the ulnar bursa and middle palmar space from the side, all beautifully illustrated by Miss Zita Stead. Professor Henry's work owes much to experience shared with Egyptian colleagues in Cairo in earlier years, and incorporates material discussed with students from Dominion and other countries at his well-known operative surgery classes at the British Postgraduate School. The surgical novice, and possibly the older hand also, will feel that he has been here presented with the keys of free entry to the limbs, without having to make his way in by assault.

Section headings —I Upper Limb (i) posterior humeral exposure, (ii) anterior humeral exposure, (iii) front of forearm, (iv) back of forearm, (v) approaches to hand. II Lower Limb (i) subgluteal exposure, (ii) anterior femoral exposure, (iii) popliteal exposure, (iv) back of thigh, (v) midline popliteal route, (vi) back of leg, (vii) front of leg and anterior tibial arch, (viii) fibula and peroneal nerves, (ix) plantar exposure.

A HANDBOOK OF GYNAECOLOGY for the Student and General Practitioner

by Bethel Solomons and E. Solomons Fourth edition London, Baillière, Tindall & Cox, 1944 352 pages, 280 illustrations 20 x 13 cm £1.5s [£1.25]

The author of this book, who is a former master of the Rotunda Hospital, Dublin, believes that students of gynaecology need only a *small* book to aid them in practical work, provided that such a book is read in conjunction with comprehensive teaching in the hospital.

In the present edition of this work the author has been assisted by E. Solomons, assistant gynaecologist to Dr Stevens' Hospital, Dublin, and a chapter on x-rays and radium in gynaecology has been contributed by Dr Oliver Chance. Although war conditions have created difficulties in the revision of the book, most of the chapter on anatomy has been rewritten, the chapter on hormones has been revised and the latest work on leucorrhoea is given. The subject of ectopic gestation is included, as being concerned as much with gynaecology as with obstetrics, the chapter on ovarian tumours has been brought up to date and the section on vaginal hysterectomy has been amplified. A number of new illustrations has been included.

Contents (i) anatomy and development of the female genital organs, (ii) introduction to gynaecology, examination of the patient, (iii) introductory terms and their significance (menstruation, conception, etc.), (iv) inflammations (including gonorrhoea and tuberculosis), (v) tumours, (vi) gynaecological lacerations, malformations and displacements, (vii) other pathological gynaecological conditions, (viii) the use of certain gynaecological instruments, (ix) operations, (x) radium and x-rays in gynaecology.

A SHORT PRACTICE OF MIDWIFERY FOR NURSES

by Henry Jellett. Thirteenth edition London, J & A. Churchill, Ltd, 1945. 456 pages, 190 illustrations 18 x 12 cm 12s 6d [£0.625]

This book lays great emphasis on adequate ante-natal care and the importance of aseptic management of labour and the puerperium. These two principles are an essential part of the basis upon which a midwife's practice is built. The preface includes a

table showing that the application of these principles in New Zealand maternity hospitals has been followed by a drop in the maternal death rate from sepsis from 2.01 per 1,000 live births in 1927 to 0.44 in 1942.

Two chapters are devoted to the care and feeding of infants. The book is well produced, profusely illustrated, and contains a useful glossary of medical terms.

Chapter headings: (i) asepsis in midwifery, (ii) elementary pelvic anatomy—menstruation and conception, (iii) the ovum, (iv) obstetrical diagnosis, (v) the phenomena and diagnosis of pregnancy, (vi) ante-natal care, (vii) labour and its phenomena, (viii) vertex presentations, (ix) the preparations for labour, (x) the management of normal labour, (xi) face presentation—

brew presentation, (xii) pelvic presentation, (xiii) transverse presentation, (xiv) multiple pregnancy, (xv) the puerperium, (xvi) the disorders of pregnancy—venereal disease, (xvii) diseases of the decidua and ovum, (xviii) the toxæmias of pregnancy, (xix) abortion—miscarriage—premature labour—delayed labour, (xx) extra uterine pregnancy, (xxi) ante partum haemorrhage, (xxii) precipitate labour—uterine inertia—retained placenta, (xxiii) contracted pelvis, (xxiv) arrested breech—impacted shoulders—prolapse of the cord, (xxv) obstructed delivery, (xxvi) post-partum haemorrhage, (xxvii) general injuries, (xxviii) sapraemia and septic infection, (xxix) diseases associated with the puerperium, (xxx) obstetrical operations, (xxxi) the infant—infant feeding, (xxxii) infantile disorders and diseases.

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FILMS

(Overseas medical teachers and medical societies who wish to borrow or purchase prints of the films indexed or reviewed here should apply to the nearest British Council representative (see inside back cover) or direct to the Editor, quoting the numbers used below, e.g. Film 10. Inclusion of a film in this section does not imply that a print will be available for loan or purchase. In some cases it will be, and in others it will not.)

10

HOSPITAL SCHOOL

made by Spectator Short Films, Ltd., 1943, owned by British Council, 16 mm sound, 400 ft. [120 m.], 35 mm sound, 989 ft [300 m.], 2 reels, black and white, 11 minutes.

This film illustrates the work of Lord Mayor Treloar Hospital School, which admits each year 400–500 crippled children up to the age of 16 years, and is the largest establishment of its kind in Great Britain.

Sequences are included showing the operating theatre, x-ray department, plaster-room (Fig. 1), physiotherapy department, the

exercise-room, where there are special machines to help cripples to learn to walk (Fig. 2), and the warm pool, which is of special value to children whose limbs are too paralysed to move against the bedclothes (Fig. 3).

The buildings are designed to use natural sunlight to the fullest advantage. Schoolwork goes on as usual, as many of the classes as possible being held in the open air (Fig. 4). Many of the boys learn trades at a special training-school attached to the hospital. The companionship and normal atmosphere at the Treloar hospital is good for the mental outlook of the crippled child.

This film is suitable for general and medical audiences.



1 Plaster cast being removed
3 Treatment in warm pool

2 Taking exercise and learning to walk.
4 Continuing lessons while in hospital.

11

CONTRACTION OF THE SPLEEN

made by J. Yule Bogue, 1941, owned by J. Yule Bogue, 16 mm. silent, 100 ft. [30 m.], 1 reel, Kodachrome, 7 minutes.

This film is an excellent example of the intelligent use of the film in medical teaching. It has been made by the secretary of the Physiological Film Library who has made a special study of the applications of cinematography to physiological teaching and research.

The purpose of the film is to demonstrate the contraction of the spleen following the administration of a vaso-constrictor (adrenaline) and a vaso-dilator (amyl nitrite). The first shot shows the

effect of an intravenous injection of adrenaline on the extensorized spleen of a dog—it contracts without appreciable colour-change. This is followed by a similar experiment on a cat. A split-screen shot enables the audience to compare the same spleen before and after adrenaline.

Amyl nitrite inhalation also results in contraction of the spleen, but there is also a marked colour change. This is demonstrated in the cat by means of two split-screen shots, the first showing the spleen before and after amyl nitrite, the second comparing the adrenaline-contracted with the amyl nitrite-contracted spleen. To demonstrate the mode of action of amyl nitrite, about one-half of the spleen is denervated. Amyl nitrite inhalation now results

in contraction only of the innervated half, thus indicating that the splenic contraction following amyl nitrite is a reflex due to the fall in blood-pressure. The change in colour is due to the poor oxygenation of the blood owing to pooling and reduced venous return, and to the formation of nitrosohaemoglobin

12

SCABIES

made by Spectator Short Films, Ltd., 1943; owned by Ministry of Information for Ministry of Health; 16 mm. sound, 1,340 ft. [400 m], 35 mm sound, 3,310 ft [990 m]; 3 reels, black and white, 36 minutes

With the outbreak of war there was a progressive rise in the incidence of scabies. A similar increase was also observed during the war of 1914-18. This increase in incidence is common to all countries where statistics are available.

The film was made for the Ministry of Health for the purpose of helping doctors, nurses, and others concerned to combat this parasitic skin-infection according to the most modern methods. There is excellent cine-photomicrography and diagrammatic representation demonstrating the life-cycle and the habits of the sarcoptes. The modes of conveyance of the infection from one person to another, the types of eruption in adults and in children, and the association of secondary skin-infections with scabies, are all clearly demonstrated. Complete details of treatment are given

and it is emphasized that it is useless to treat the individual and to neglect his contacts.

This film was made primarily for exhibition in Britain and references to Ministry of Health circulars, prices of drugs, etc., are of purely domestic interest and would have no meaning for an overseas audience.

The film is suitable for showing to doctors and medical auxiliaries, but would not be suitable for a mixed lay audience.

13

SCABIES MITE

made by Byron Films Ltd, 1943; owned by Ministry of Information for Ministry of Health; 16 mm. sound, 250 ft [70 m]; 35 mm sound, 620 ft. [190 m], 1 reel; black and white; 7 minutes.

The purpose of this film is to show in greater detail than in the film "Scabies" [BMB 796/12], the life-cycle of the female sarcoptes. Clear diagrams and good cine-photomicrography illustrate the newly-fertilized female making the burrow in the horny layer of the skin, where her eggs will be deposited. The larval parasites, which hatch from the eggs in about 3 days, are shown after migration to the surface of the skin, digging into neighbouring hair-follicles. Immature male and female sarcoptes are seen, the female type after impregnation increasing to its mature size and starting the cycle again.

This film is of general medical and biological interest.

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